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LITERATURE REVIEW

Osteopontin and Its Clinical Correlation to Type 1 Cardiorenal Syndrome: A Literature Review

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ABSTRACT

Cardiorenal syndrome (CRS) is a spectrum of disorders involving both the heart and the kidneys, either acutely or chronically, in one organ that can lead to dysfunction in the other. Type 1 CRS, the most common CRS, is when acute heart dysfunction impacts acute kidney dysfunction, commonly known as acute kidney injury. Comorbidities involving these two significant organs contribute to a high patient mortality rate that requires a new potential diagnostic method. Biomarkers are one of the diagnostic modalities widely used in various diseases. Osteopontin (OPN) is a phosphorylated glycoprotein found primarily in bones and teeth that regulates mineralization. Osteopontin is known to be involved in describing various pathological changes in the body, including cardiovascular diseases. This review aims to evaluate the clinical correlation of OPN level changes with the occurrence of Type 1 CRS. The results indicate that OPN also plays a role in detecting the progression of cardiovascular disease towards renal injury. The imbalance in the function of OPN as a pro-inflammatory and anti-inflammatory agent increases the progression of kidney disease in patients. Further findings suggest that, more specifically, urinary OPN describes renal injury events in type 1 CRS patients.

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INTRODUCTION

A variety of conditions affecting the heart and kidneys that can cause acute or long-term dysfunction in one organ might result in acute or long-term malfunction in the other, which is known as cardiorenal syndrome (CRS). Generally, there are five forms of CRS depending on which main organ is affected and how chronic the condition is. Type 1 cardiorenal syndrome is the most prevalent form of cardiorenal syndrome. Types 1 and 2 of cardiorenal syndrome refer to acute heart dysfunction that affects kidney function, leading to both acute and chronic kidney disorders (Uduman, 2018). Several earlier studies have reported that the prevalence of cardiorenal syndrome type 1 in patients with acute decompensated heart failure (ADHF) can reach 32% to 40% (Roy et al., 2013). It has been reported that 25–63% of heart failure patients also experience renal dysfunction to the extent that they may require dialysis therapy (Ronco & Di Lullo, 2016). A study by Mavrakanas et al. (2017) also revealed that the risk of death in acute CRS (such as CRS type 1) is higher than in CKD patients without CRS. According to Hu et al. (2016), the mortality rate due to type 1 cardiorenal syndrome has reached 23.2%. According to Pimienta González et al. (2016), mortality due to type 1 CRS has been associated with 56.6% of all documented death events in patients with acute coronary syndrome. Renal and cardiovascular disease are known to be closely related. Renal function might deteriorate due to several risk factors, including diabetes and hypertension. One of the most significant risk factors contributing to the decline in renal function (WRF) is atherosclerosis. When referring to patients with type 1 cardiorenal syndrome, the phrase "worsening renal function" (WRF) is frequently used to describe an increase in serum creatinine of more than 0.3 mg/dL (Rangaswami et al., 2019). Albuminuria and GFR can be used to measure how severe renal function has declined (Grams et al., 2010). However, the use of urinary albumin and GFR as markers for renal deterioration is not yet specific in depicting the underlying heart dysfunction. Osteopontin (OPN) is a phosphorylated glycoprotein that contributes to mineralization regulation and is present in many tissues, especially in bones and teeth. It has been discovered that this marker contributes to several pathogenic processes, such as vascular and renal illnesses (Paloian and Giachlli, 2014). The association of OPN with the progression of chronic kidney failure in patients is revealed by Kamińska et al. (2021), where a significant increase in OPN levels is found more frequently in end-stage renal disease (ESRD) patients. Nevertheless, relatively few studies still investigate the relationship between OPN levels and type 1 cardiorenal syndrome. This review aims to explore the clinical correlation between changes in OPN levels and type 1 cardiorenal syndrome.

METHOD

This study is a literature review to answer the clinical questions presented earlier. Several databases, including PubMed, ScienceDirect, and Web of Science, were used to search for literature. The studies included in this literature review encompass all research related to OPN, type 1 cardiorenal syndrome, acute kidney failure, and cardiovascular diseases. Studies will be excluded if they are in languages other than English and Indonesian.

LITERATURE REVIEW

Cardiorenal syndrome refers to a group of disorders that can damage the kidneys and heart either permanently or temporarily. If any of one organ fails, it may deteriorate the others (Rangaswami et al., 2019). The term CRS was first introduced in 2004 by the Working Group of the National Heart, Lung,

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and Blood Institute, stating that CRS is an interaction between the heart, kidneys, and vascular system that exacerbates the symptoms of heart failure (National Heart, Lung, 2004). Cardiorenal syndrome is divided into five main groups according to its types. Acute kidney dysfunction is a result of an acute decrease in heart function, which is known as cardiorenal syndrome type 1. A similar pattern is seen in cardiorenal syndrome type 2, in which persistent heart failure leads to chronic kidney impairment. Cardiorenal syndrome types 3 and 4 represent the phenotypes of renocardiac syndrome, where type 3 refers to acute kidney dysfunction impacting acute heart dysfunction, while type 4 refers to more chronic conditions. Cardiorenal syndrome type 5 is a secondary CRS where systemic processes can lead to both heart and kidney failure (Kousa et al., 2023) **(Figure 1).**

The development of CRS is linked to several intricate processes, such as endothelial cell dysfunction, anemia, atherosclerosis, chronic inflammation, diabetes mellitus, hypertension, and abnormalities in iron metabolism. (Rangaswami et al., 2019). Acute kidney injury (AKI) is the primary clinical outcome that occurs in patients with cardiorenal syndrome type 1 (Ronco et al., 2012). In 2002, the Acute Dialysis Quality Initiative defined the spectrum of acute kidney injury (AKI) using the RIFLE criteria (risk, injury, failure, loss of kidney function, and end-stage kidney disease) (Rangaswami et al., 2019). Measuring urine output and serum creatinine is the typical procedure for diagnosing acute renal injury. It is necessary to diagnose acute kidney injury problems resulting from low estimated glomerular filtration rate (eGFR), such as acute heart failure patients, using clinical and

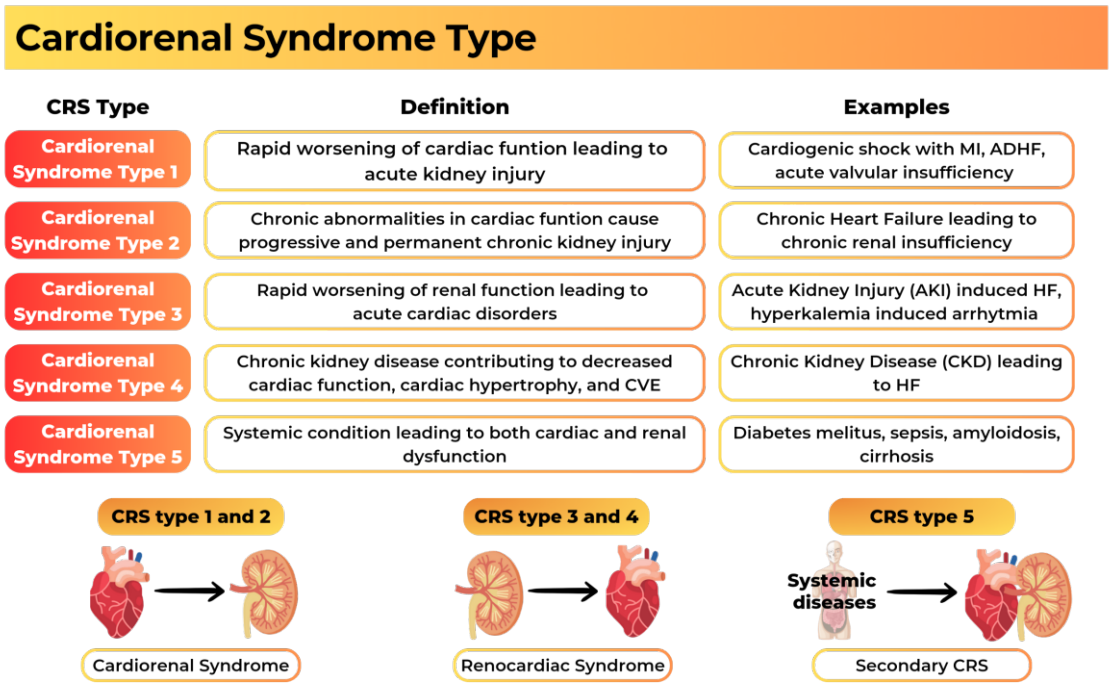

Figure 1. Type of Cardiorenal Syndrome

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analytical methods. However, using existing urine and serum biomarkers still can't optimally depict the state of renal injury (Fu et al., 2021). Therefore, current advancements in biomarkers are expected to represent organ injury more accurately, proving valuable in future therapeutic strategies for CRS patients.

Cardiorenal Syndrome Pathophysiology

The pathophysiological basis of cardiorenal syndrome is the failure of the heart to meet the body's circulatory needs, leading to renal hypoperfusion. Reduced blood flow to the kidneys triggers the activation of the renin-angiotensin-aldosterone system (RAAS), the sympathetic nervous system, and the secretion of antidiuretic hormone (ADH). This process increases preload and causes fluid retention, which impairs the heart's ability to pump blood (Rangaswami et al., 2019). To improve the glomerular filtration rate (GFR), the tone of the efferent arteriole muscles is also increased in response to renal hypoperfusion. However, in severe heart failure conditions, this compensatory effort is lost, leading to a more significant decrease in GFR due to elevated levels of RAAS and neurohormonal activation (Rangaswami et al., 2019). The concentration-dependent effects of angiotensin II explain this. Low blood levels of angiotensin II increase the GFR by enhancing the tone of the efferent arteriole. However, when the levels of angiotensin II are sufficiently high due to excessive activation of the RAAS system in patients with impaired cardiac contractility, it tends to decrease GFR by constricting both afferent and efferent arterioles (Maranduca et al., 2023). Renal damage is further promoted by high levels of angiotensin II, which also causes the kidneys to release endothelin-1, a vasoconstrictor with pro-inflammatory and profibrotic properties. (Kumar et al., 2019).

Angiotensin II, the primary mediator in the RAAS, also induces several pathological changes in the heart. Type 1 angiotensin II receptors in the heart lead to the release of transforming growth factor-β1 and ET-1 from fibroblasts, triggering myocardial cell hypertrophy (Kumar et al., 2019). Angiotensin II also contributes to inflammation and hypertension by increasing the production of reactive oxygen species. It worsens heart function and circulation (Triposkiadis et al., 2009). Furthermore, the reduction in renal blood flow will be compensated by increased sodium and water absorption, further worsening patient congestion. This also explains why serum creatinine levels are found to increase in patients with kidney dysfunction. Another compensatory mechanism involves an increase in arginine vasopressin peptide (AVP) secretion due to decreased vascular volume, which acts through V2 receptors in the collecting duct. However, heart function will be further impaired by this. It has been discovered that left ventricular dysfunction is linked to elevated AVP levels (Gilotra, 2014). The level of AVP is also directly proportional to the progression of chronic kidney failure in patients through its hemodynamic effects, which can enhance the activation of the RAAS system by increasing renin secretion (Afsar, 2017).

In patients with heart failure, systemic backflow will also raise intra-abdominal pressure, which increases central venous pressure. A gradient between arterial and venous pressures is necessary to maintain organ perfusion. In patients with acute decompensated heart failure, central venous pressure (CVP) will decrease renal perfusion and cause renal compression, further worsening the patient's kidney function (Kumar et al., 2019; Rangaswami et al., 2019). The reduction in renal perfusion ultimately has two significant impacts: a decrease in the vascularization of renal parenchyma and a

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reduction in renal oxygen partial pressure, ultimately leading to renal injury.

Elevated oxidative stress is another factor supporting the development of cardiorenal syndrome in individuals. When free radicals and the body's antioxidant defenses are out of balance, some molecules oxidize and change in structure and function. This is known as oxidative stress (Liakopoulos et al., 2017). Increased oxidative stress results from injury and inflammation processes that impact the changes in energy metabolism in cardiac myocytes. The production of ATP in the heart, primarily derived from fatty acid oxidation, shifts to glycolysis, generating less energy and thereby increasing the risk of myocyte injury and apoptosis (Kumar et al., 2019). This heart dysfunction ultimately leads to the failure of organ and renal perfusion.

The diagnosis of patients with suspected cardiorenal syndrome can be performed using various modalities, considering the complexity of the pathophysiology of this disorder. Modalities used may include biomarker assessment, non-invasive imaging, invasive hemodynamic monitoring, additional supportive examinations, and clinical evaluation of the patient (Rangaswami et al., 2019). More and more research is being done on using biomarkers to identify cardiac and renal damage. These biomarkers can identify kidney, heart damage, or both.

Cardiac markers used in CRS patients are often based on heart failure biomarkers, with BNP (Brain Natriuretic Peptide) and NT-pro BNP being commonly utilized. Previous studies have also indicated that BNP concentrations are found to be elevated and strongly associated with the occurrence of chronic kidney failure (Schneider et al., 2023). Brain natriuretic peptide levels are also significantly elevated in CRS patients compared to heart failure patients without renal impairment (Palazzuoli et al., 2014). Several other cardiac markers have been demonstrated by various studies, such as Galectin-3, troponin I and T, and suppressor of tumorigenicity 2 (ST2). Galectin-3 has been significantly identified as a predictor of cardiovascular mortality and incidents of renal dysfunction in a study involving 1,201 patients (Caravaca Perez et al., 2022). The concentrations of troponin T and I are also higher in patients with an increased stage of chronic kidney disease (CKD), irrespective of a history of previous heart disease (Bjurman et al., 2015). Suppressor of tumorigenicity 2 (ST2) also exhibits a similar pattern, with elevated levels significantly found in patients with chronic kidney failure (Gungor et al., 2017).

Research on renal markers for the early detection of cardiorenal syndrome has yielded more findings than cardiac markers. These include serum creatinine, CysC, NGAL, KIM-1, NAG, IL-18, L-FABP, and others. The selection of renal markers for detection is divided based on the marker's capabilities, namely markers that can depict glomerular integrity through eGFR and portray tubular injury. Some traditional markers, like serum creatinine, albuminuria, and CysC, are commonly used. However, these three still have limitations and potential bias risks when used for cardiorenal syndrome detection (Dupont et al., 2013). Some markers capable of depicting tubular injury, such as NGAL, KIM-1, and TIMP-2, are supported for their use in determining the progression of heart failure in patients suspected of having cardiorenal syndrome. A study by Mortara et al. (Mortara et al., 2013) demonstrates that NGAL concentrations increase progressively in patients with acute heart failure and progressive acute kidney failure, as evidenced by an AUC value of 0.91. A cross-sectional study also revealed that an elevation in urinary

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KIM-1 levels is associated with a decline in eGFR and an increase in albuminuria, indicating worsening kidney function (Waikar et al., 2016). TIMP-2 has also been found to play a role in the pathogenesis of acute kidney injury (AKI) and is considered a potential therapeutic target in the future (Wen et al., 2020). Imaging modalities for detecting heart and kidney abnormalities are routine, including echocardiography, intrarenal Doppler ultrasound, CT scans, and MRI.

Osteopontin

Osteopontin (OPN) is a phosphorylated glycoprotein found in various tissues, primarily bone and teeth (Paloian & Giachelli, 2014). Osteopontin was introduced as a bone-specific sialoprotein first cloned in mouse sarcoma cells (Wolak, 2014). In humans, osteopontin is present in different cells and tissues at various concentrations, such as the salivary glands, bone marrow, kidneys, dental tissue, macrophages, smooth muscle, striated muscle, mammary gland cells, chorionic villi, uterine decidua layers, pancreatic ducts, bile, and urine. (Icer & Gezmen-Karadag, 2018; Uaesoontrachoon *et al*., 2013). OPNs are increasingly used as diagnostic and prognostic markers, including for cardiorenal diseases. Elevated OPN levels are known and are estimated to correlate with various cardiovascular diseases, both acute and chronic. Patients with acute congestive heart failure and acute coronary syndrome are found to have higher levels of OPN (Behnes *et al*., 2013; Cheong *et al*., 2023). In more chronic conditions, chronic heart failure also increases OPN levels (Rosenberg *et al*., 2008).

Osteopontin is also present physiologically in the distal tubules of the nephron and the loop of Henle. When renal damage is present, OPN levels will rise. (Taub *et al*., 2012). Hyperfiltration in patients with kidney failure can also lead to the activation of the RAAS system, including angiotensin II, which stimulates OPN production in the glomerulus. Elevated levels of OPN in acute kidney injury have also been previously reported by several studies. Lorenzen *et al*. (2010) found that OPN performs well in depicting deterioration in acute kidney injury patients with a sensitivity of 100%, specificity of 61%, and an AUC of 0.82. Furthermore, the risk of developing end-stage kidney disease increases in patients with increased OPN levels, with an HR of 1.42 (95% CI 0.74-2.7) (Kamińska et al., 2021). This further supports the current research to explore the correlation between OPN levels and type 1 cardiorenal syndrome.

Osteopontin and Cardiorenal Syndrome Type 1

Osteopontin consists of 314 amino acid residues with a molecular weight of 32,600 kDa and plays a primary role in mineralization regulation. Osteopontin works by inhibiting mineralization through the activation of osteoclasts and the inhibition of hydroxyapatite formation (Roumeliotis *et al*., 2020). Physiologically, OPN is secreted in small amounts into circulation. The presence of myocardial infarction will trigger the release of OPN from macrophages infiltrating the myocardium into circulation (Shirakawa *et al*., 2018). Osteopontin will enhance macrophage phagocytosis to clear necrotic tissue and promote fibrous tissue formation through myofibroblast differentiation stimulation (Shirakawa & Sano, 2021). The increase in OPN, in the end, can depict the presence of heart injury and dysfunction.

The most frequent cause of anatomical and functional problems in the heart that ultimately contribute to sudden heart failure is myocardial infarction. Type 1 cardiorenal syndrome, which causes acute kidney injury, is primarily brought on by acute heart failure

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(AHF). Previous studies have shown that plasma OPN levels are significantly higher in patients with AKI (Lorenzen *et al*., 2010).

In normal conditions, OPN is expressed by renal tissue in both fetal and adult individuals and interacts with the surrounding tissue mediated by αvβ3 and αvβ5 integrins. Both adhesion molecules can be found in the Bowman's capsule and glomerular epithelium. The distal tubules are also known to express the CD44 receptor for OPN (Kaleta, 2019). In experimental animals, OPN plays a role in processes that lead to renal damage (Pei *et al*., 2016). OPN can induce macrophage chemotaxis through NF-kB activation and increase OPN production in various cells. This will trigger increased macrophage infiltration in kidney tubular and interstitial cells, leading to fibrosis. These findings are supported by previous research revealing that OPN levels were found to proportionally increase in patients with coronary heart disease with worsening renal function (Chen *et al*., 2014).

Patients with chronic kidney failure are commonly accompanied by progressive renal tissue fibrosis, which is suspected to be mediated by OPN (Lorenzen *et al*., 2010). This can be explained by the pathophysiological basis of type 1 cardiorenal syndrome, where renal hypoperfusion due to acute heart failure leads to renal hypoxia and injury. The compensation from the RAAS system is one factor that drives increased OPN secretion. The high levels of angiotensin II in response to the RAAS system's activation will increase the OPN levels. This is further supported by Wolak et al. (2009), stating that the function of angiotensin II is inhibited in the presence of antibodies against OPN. In general, osteopontin works by aiding in the recruitment of T cells and macrophages engaged in the inflammatory process. Kidney fibrosis in the matrix and interstitial spaces can result from inflammation and elevated oxidative stress. The induction of nitric oxide (NO) synthase and activation of NADPH oxidase will increase cytotoxic peroxynitrite production. Peroxynitrite is generated from the interaction between superoxide anions and NO. Fortunately, the clinical significance of increased OPN levels is evident, as OPN can suppress peroxynitrite production, triggering increased fibrosis and kidney dysfunction (Wolak et al., 2009). Additionally, OPN has been proven to inhibit the production of oxidative molecules involved in kidney damage, such as NOX2, NOX4, and MCP-1 (Trostel et al., 2018). Other findings indicate that OPN can inhibit the production PAI-1, thus inhibiting interstitial fibrosis. Osteopontin's action on urokinase tissue plasminogen activator (uPAR) also inhibits tubular cell apoptosis, reducing tubular cell atrophy. As a result, OPN has two different effects on renal damage: it induces damage and inhibits it. The unbalanced interplay between these pro- and anti-inflammatory consequences leads to the deterioration of renal function in individuals. (Grande et al., 2010) **(Figure 2)**.

Following this, both the blood and the urine will start to release osteopontin, which makes both samples helpful for identifying renal impairment in patients. When acute kidney injury progresses in individuals with cardiovascular illness, the concentration of OPN is higher than in patients with cardiovascular disorders alone. Previous studies have shown that both plasma OPN and urine OPN are significantly associated with AKI, but urine OPN has better specificity than plasma OPN. Meanwhile, plasma OPNs have better specificity in depicting cardiovascular disorders (Askenazi *et al*., 2012; Feldreich *et al*., 2017). This indicates that OPN has the potential to be a marker for diagnosing type 1 cardiorenal syndrome. However, this review still has some limitations. Firstly, few studies discuss OPN concentrations in patients with

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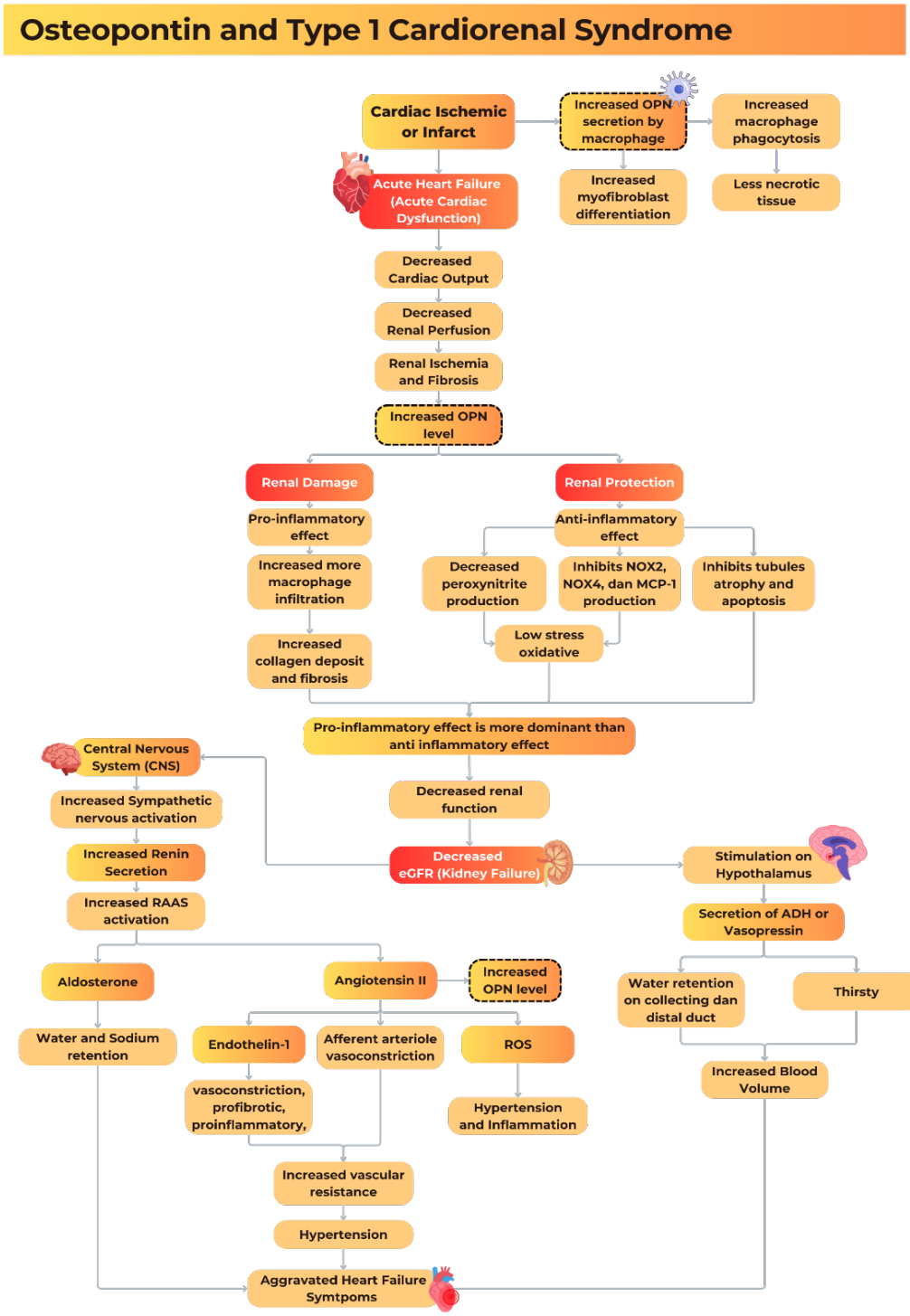

Figure 2. Type 1 cardiorenal syndrome pathophysiology and its correlation to OPN level.

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cardiorenal syndrome. Secondly, some findings reported in this review might also apply to other types of cardiorenal syndrome. Thirdly, OPN concentrations that can depict the risk of cardiorenal syndrome events have not been widely reported. Therefore, further research on the relationship between OPN and cardiorenal syndrome must be pursued.

CONCLUSION

Osteopontin is a biomarker found in urine and plasma that can depict various pathological changes in the body. The results indicate that OPN can depict the pathological conditions of heart dysfunction leading to acute kidney damage due to hypoperfusion, hypoxia, and renal injury. The imbalance in the function of OPN as a pro-inflammatory and anti-inflammatory agent can increase the progression of kidney disease in patients. The deposition of fibrous and collagen tissue that occurs in the renal parenchyma cannot be neutralized by defense mechanisms that are also stimulated by OPN, thus promoting renal injury. Further findings suggest that the increase in urine OPN is more specific in depicting acute renal injury in type 1 cardiorenal syndrome. In contrast, the increase in plasma OPN is more specific in describing the risk of cardiovascular events. Nonetheless, research confirming OPN's continuous effectiveness in diagnosing and prognosis type 1 cardiorenal syndrome remains scarce. Therefore, further research is still required to support these findings.

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