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Serum Procalcitonin (PCT) Level In Acute Kidney Injury (AKI) In Critical Patients

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ABSTRACT

Early prediction and avoidance of aggravation of AKI will be useful in identifying patients at risk of developing a higher degree of AKI. Many studies have been conducted to prevent AKI and find biomarkers to predict AKI. Many studies have identified biomarkers of AKI, such as neutrophil-associated lipocalin (NGAL), cystatin C, interleukin-18, and tissue inhibitors of metalloproteinase-2 (TIMP-2). Yet few have investigated the role of PCT as a predictor of AKI. The pathophysiological mechanisms that explain the association between serum PCT and AKI remain unclear. Various inflammatory responses are thought to play a role in the AKI development. PCT acts as a chemoattractant in the inflammation area and causes more monocytes to invade the inflammation. PCT is initially produced in adherent monocytes and then contributes to an increase in circulating PCT by attracting parenchymal cells as they attach directly to activated monocytes. High PCT levels ultimately act as a direct chemoattractant to monocyte counts.

Keywords

PCT, AKI, Early prediction

INTRODUCTION

Acute kidney injury (AKI) occurs in about 5-7% of patients hospitalized and occurs in about 36-57% of critically ill patients admitted to the intensive care unit (ICU) [1–3]. AKI in critically ill patients in the ICU can occur due to the etiology of the underlying disease, such as sepsis, trauma, and major surgery. But the AKI condition that occurs is associated with high mortality and significant morbidity AKI is an independent risk factor for mortality up to 70% in patients critically with the higher the degree of AKI, the higher the mortality [1].

Early prediction and avoidance of aggravation of AKI will be useful in identifying patients at risk of developing a higher degree of AKI. Many studies have been conducted to prevent AKI and find biomarkers to predict AKI [4, 5]. Experimental studies about ischemic reperfusion, septic endotoxemia, and nephrotoxins models have shown a potent inflammatory component that is associated with AKI. It is responsible for initiating severe AKI developments [6]. Many studies have identified biomarkers of AKI, such as neutrophil-associated lipocalin (NGAL), cystatin C, interleukin-18, and tissue inhibitors of metalloproteinase-2 (TIMP-2). Yet few have investigated the role of PCT as a predictor of AKI [7]. Recent studies have shown an increased level of PCT in AKI patients, a biomarker of inflammation, and is widely used in the ICU as a biomarker of bacterial sepsis and response to antibiotic therapy. Recent studies have shown an increased level of PCT in AKI patients, a biomarker of inflammation, and is widely used in the ICU as a biomarker of bacterial sepsis and response to antibiotic therapy [8].

According to research by Chun et al. (2019), increased procalcitonin levels increase the risk of AKI by 1.7 to 2.4 times, with higher PCT levels found in AKI patients compared to non-AKI [9]. Other studies have also shown that in univariate and multivariate analyzes. Regarding predictors of AKI, that increased PCT was an independent predictor of AKI, about 4.4 times the likelihood of AKI. However, Rodriguez et al. (2016) reported different results that PCT cannot be used as a biomarker of AKI. This study concluded that the AKI and non-AKI patients were reported to have the same median PCT value in postoperative cardiac surgery patients [10].

Procalcitonin, a precursor of the peptide hormone calcitonin with a molecular weight of about 13 kD, is used to differentiate bacterial infections such as sepsis and non-bacterial infections. The Surviving Sepsis Campaign (2016) no longer recommends PCT as a sepsis biomarker and provides only weak recommendations [11]. Research reports on PCT found that PCT levels had increased, especially in septic patients with AKI, so the study concluded that increased PCT showed a strong relationship with increased PCT level development of AKI in septic patients [12]. The mechanism by which PCT contributes to the development of AKI is not fully understood. Previous studies have shown that bacterial toxins can induce PCT. It can directly mediate cytotoxins to mesangial cells via increased synthesis of pro-inflammatory cytokines [13]. In addition, PCT has also been shown to act as a chemoattractant against monocytes and high levels of PCT result in a large number of monocytes at the site of infection and contribute to injury, especially in the glomerulus. This is evidenced by the significant correlation between increased PCT levels and increased creatinine and decreased glomerular filtration rate [14–16]

PROCALCITONIN BIOSYNTHESIS

Procalcitonin is a polypeptide precursor of the CT hormone derived from the thyroid gland. CT plays a role in responding to the effects of hyper or hypocalcemia. PCT is a protein composed of 116 amino acids (AA) with a molecular weight (BM) of ± 13 kiloDalton (kDa). It encodes the Calc-I gene located on chromosome 11 and is produced in C cells of the thyroid gland as a prohormone from calcitonin consisting of 3 peptides. Namely 57 AA at the amino end of the group (N ProCT), 32 AA CT immature containing glycine, and 21 AA CT at calcitonin-terminus peptide-1 (CCP-1). The normal serum contains Pro PCT, Free N Pro CT, Free CCP-1, and Free CT-CCP-1 peptides [17–19]

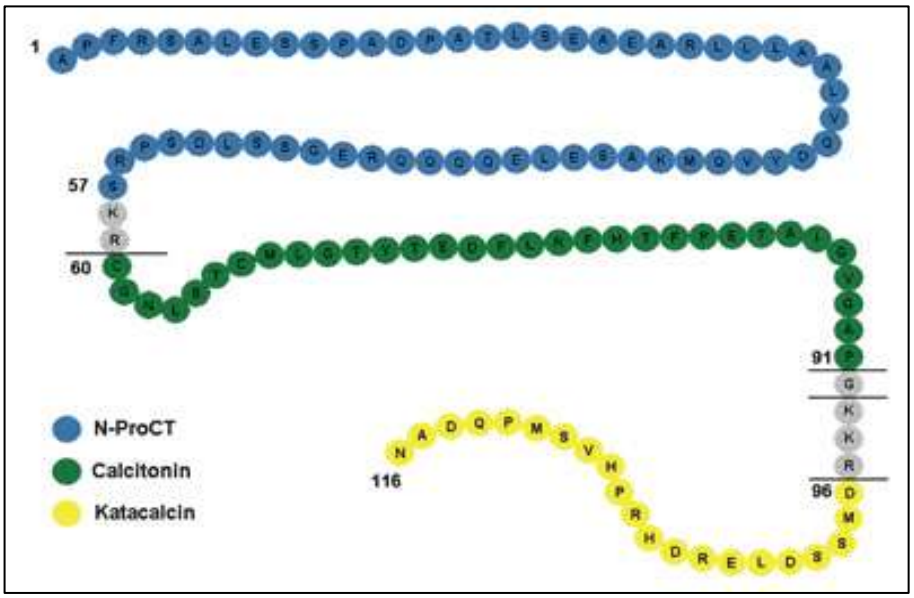

Figure 1. Primary Structure of 116-kD Polypeptide Precursor Calcitonin [20]

The Calc-I gene produces two different transcriptions by tissue-specific alternative splicing. The first is derived from exons 1-4 of the 6 exons as the code for prePCT, a peptide chain consisting of 141 AA which

has a peptide chain consisting of 25 hydrophobic AA signals. In thyroid gland C cells, the proteolytic process produces an N-terminal fragment (57 AA), CT (32 AA), and katacalcin (21 AA). The presence of the signal peptide allows PCT to be entirely secreted after glycosylation by other cells. The second transcript is selectively cut containing exons 1,2,3,5,6 and is the code for Calcitonin Gene-Related Peptide (CGRP), where CGRP is widely expressed in nerves in the brain, blood vessels, and gastrointestinal tract. CGRP has a role in immunomodulation, neurotransmitter, and vascular control [21, 22].

CTmRNA levels obtained in sepsis function as endocrine glands that produce CTpr (CT precursor). The increase occurs in the liver, lungs, kidneys, pancreas, brain, heart, and small intestine. The increase in PCT values in septic thyroidectomy suggests that thyroid C cells are not the only site of origin for PCT. PCT secretes all the products of the biosynthetic pathway. It has been detected in the homogeneity of small cell carcinoma in human lungs. PCT mRNA is expressed in human peripheral blood mononuclear cells and various proinflammatory cytokines. And LPS has stimulatory effects. Approximately one-third of unstimulated human lymphocytes and monocytes contain immunologically explicable PCT proteins, a condition triggered by bacterial LPS, but monocytes from patients with septic shock exhibit elevated basal values and elevated LPS-stimulated PCT levels [23, 24]

Specific proteolysis failure in severe bacterial infection or sepsis results in precursor protein high concentrations, and PCT fragments accumulate in the plasma. The origin of inflammation-stimulated PCT synthesis is currently unclear. Neuroendocrine cells in the lung or gut are currently considered the primary source of PCT. Because patients with total thyroidectomy are still capable of producing PCT in the setting of sepsis. PCT can increase 2-3 hours after induction and to several hundred ng/ml with the molecular state being very stable in vitro or in vivo [21, 24].

The results of PCT induction in animal experiments showed that: [25]

1. In septic animals within 24 hours, PCT increased relatively high, and IL-1β and TNF-α increased twice.
2. Sepsis animals are given PCT also did not show an increase in IL-1β and TNF-α.
3. Healthy animals that were also given PCT also showed no response to IL-1β and TNF-α
4. Healthy animals with the addition of TNF-α, have seen an increase in PCT up to twenty-five times.

Plasma production of PCT can be induced in healthy humans by injection of low LPS. The increase in PCT concentration was detected for the first time 2 hours after endotoxin injection, and within 6 to 8 hours PCT levels would increase and reach stable levels within ± 12 hours. After 2-3 days, PCT levels will return to normal. Specific and rapid induction by an adequate stimulus will lead to high production of PCT in patients with severe bacterial infection or sepsis. This situation demonstrates the pathophysiology of PCT in the acute immune response [22, 23, 25].

PCT in healthy people is altered, and no residue is released into the bloodstream, therefore PCT levels are undetectable (< 0.1 ng/ml). In severe infections with systemic symptoms, PCT levels can exceed 100 ng/mL. In contrast to the half-life of CT, which is only 10 minutes, PCT has a long half-life of 25-30 hours [17, 18].

ACUTE KIDNEY INJURY (AKI)

Acute Kidney Injury (AKI) is a rapid decrease (within hours to weeks) of glomerular filtration rate (GFR), which is generally reversible, followed by kidney failure to excrete nitrogenous metabolic wastes, with or without disturbances in fluid and electrolyte balance. The Acute Dialysis Quality Initiative (ADQI) consists of nephrologists and intensivists in America. Who agreed to change the term ARF to AKI in 2002. The replacement of the term renal to the kidney is expected to help the general public understand, while the replacement of the term failure to injury is considered to more accurately describe the pathology of kidney disorders [26, 27].

Initial evaluation and management of patients with acute kidney injury (AKI) should include: [28, 29]

1. Assessment of causes contributing to kidney injury
2. Assessment of clinical course includes comorbidities

3. Careful assessment of volume status
4. Appropriate therapeutic measures are designed to treat or prevent the worsening of functional or structural renal abnormalities. The initial assessment of patients with classic AKI includes distinctions between prerenal, renal, and postrenal causes.

Acute kidney injury (AKI) is characterized by a sudden decline in kidney function that occurs within hours to days. The current diagnosis of AKI is made based on elevated serum creatinine and a decreased blood urea nitrogen (BUN) and urine output, although there are limitations. It should be noted that changes in BUN and serum creatinine may represent not only renal injury but also a normal response of the kidney to extracellular volume depletion or decreased renal blood flow [27, 30]

Table 1. Classification of AKI with RIFLE criteria, ADQI Revised 2007

Category	SCr Upgrade	Decreased GFR	UO Criteria
Risk	≥1,5 times base value	>25% base value	>0,5 ml/kg/hour, ≥6 hours
Injury	≥2,0 times base value	>50% base value	<0,5 ml/kg/ hour, ≥12 hours
Failure	≥3,0 3.0 times baseline or ≥4 mg/dl with an acute increase of ≥0,5	>75% base value	<0,5 ml/kg/ hour, ≥12 hours, or Anuria ≥12 hours
Loss	Decreased kidney function persists for more than 4 weeks		
End Stage	Decreased kidney function persists for more than three months		

Acute kidney injury was defined when one of the following criteria was met:

- Serum creatinine rises by ≥ 0,3 mg/dL or ≥ 26μmol /L within 48 hours or
- Serum creatinine increase ≥ 1,5 times the reference value, which is known or assumed to have occurred within one week or
- Urine output <0.5ml/kg/hr for > 6 consecutive hours.

ADQI issued a classification system for AKI with RIFLE criteria. It consists of 3 categories (based on increased serum Cr levels or decreased GFR or UO criteria) describing the severity of the decline in kidney function. And two categories describe the prognosis of kidney disorders as shown in table 1 [28, 30].

Table 2. Comparison of RIFLE and AKIN Criteria for the Definition of AKI [31].

RIFLE		AKIN		RIFLE/AKIN
Category	SCr or GFR	Stadium	SCr Upgrade	Changes in urine production
Risk	1.5-fold increase in SCr or 25% decrease in GFR	1	1.5-1.9-fold increase in SCr or ≥0,3 mg/dL	<0,5 mL/kg/hour for 6-12 hours
Injury	2-fold increase in SCr or 50% decrease in GFR	2	2-2.9-fold increase in SCr	<0,5 mL/kg/hour for ≥ 12 hours
Failure	3-fold increase in SCr or SCr >4 mg/dL with acute risk >0,5 mg/dL or decrease in GFR 75%	3	3-fold increase in SCr or SCr >4 mg/dL with acute risk >0,5 mg/dL or RRT	<0,3 mL/kg/hour for ≥ 24 hours or anuria for ≥ 12 hours

The Acute Kidney Injury Network (AKIN), an international collaboration of nephrologists and intensivists, proposed changes to the RIFLE criteria in 2005. AKIN seeks to increase the sensitivity of the classification with the recommendation of several modifications categories R, I, and F on the RIFLE criteria, respectively, per the AKIN criteria, stages 1, 2, and 3. Categories L and E on the RIFLE criteria describe clinical outcomes (outcomes) so that they do not include in the stages. AKI classification according to AKIN can be seen in Table 2 [28, 30].

PATHOPHYSIOLOGY

Acute Kidney Injury is the most common cause of nephrology consultation and is associated with a high mortality rate. The primary causes of AKI include ischemia, hypoxia, or nephrotoxicity. The underlying feature is a rapid decrease in glomerular filtration rate, which is usually associated with decreased renal blood flow. Inflammation represents an important additional component of AKI and causes the extension phase of the injury. And is associated with insensitivity to vasodilator therapy [32].

Sublethal alterations of renal tubular epithelial cells are crucial and have a vital impact on decreasing the glomerular filtration rate, which is a prime sign of AKI. Tubuloglomerular feedback and glomerular filtration leakage caused afferent arteriolar vasoconstriction in acute tubular necrosis. And tubular obstruction caused a decrease in the glomerular filtration rate (Fig. 2). Renal ischemia rapidly induces several structural and functional disturbances in renal proximal tubular epithelial cells. That is directly related to the conventional filamentous actin webbing in the disrupted cells. Sustained hypoxia also stimulates an inflammatory response in the kidneys leading to a further decrease in the glomerular filtration rate [32].

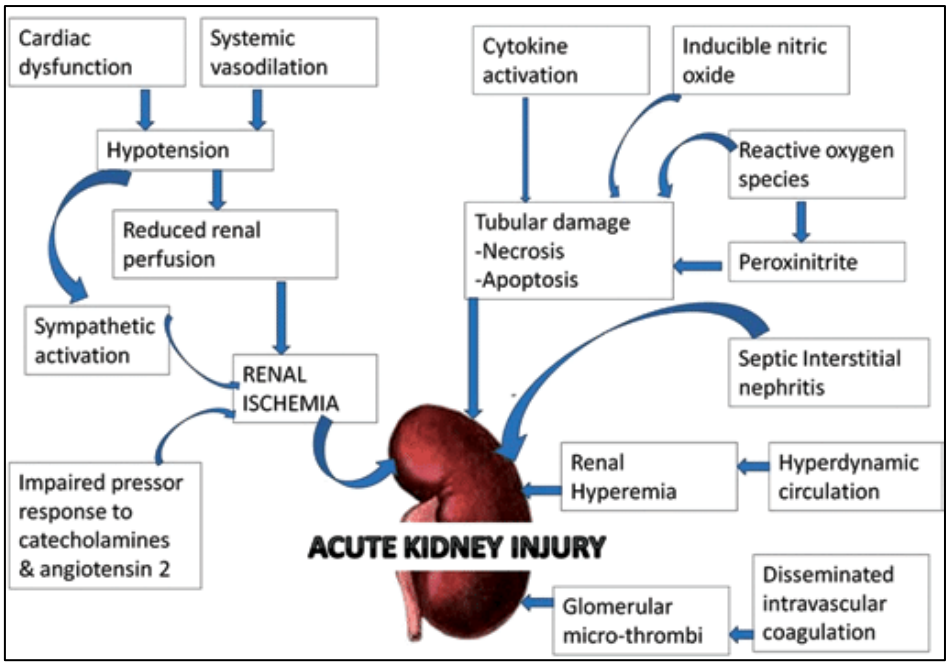

Figure 2. Pathophysiology of Acute Kidney Injury [33]

The role of hemodynamic alterations has also been highlighted in AKI, which is characterized by hemodynamic dysregulation characterized by vasomotor nephropathy. Increased renal vascular resistance by some factors causes renal blood flow disruption that results in renal hypoperfusion. Increased sympathetic nerve activity can also cause an increase in renal vascular resistance and the release of renin and angiotensin II, which are potent vasoconstrictors, leading to decreased renal blood flow. The presence of oxidative stress also contributes to an increase in renal vascular resistance [32].

Renal injury can also occur in the renal vasculature. In addition to the induction of vasoactive factors, renal injury also directly damages the renal vasculature and interferes with its activities such as affecting

vascular response, barrier function, coagulation cascade, and/or inflammatory processes. Increased sodium uptake can cause cell swelling leading to cell death, and increased extravascular pressure in the peritubular capillaries which in turn restricts blood flow. Damage to the vascular endothelium in the kidney can lead to the promotion of thrombosis and fibrin deposition, which results in ischemia. The inflammatory cascade involves proinflammatory cytokines causing damage at the cellular level in the kidney that triggers impaired kidney function [32].

THE RELATIONSHIP OF PROCALCITONIN (PCT) WITH ACUTE KIDNEY INJURY (AKI)

The clinical assessment of AKI includes a comprehensive history and examination, including the patient's volume status assessment. It is vital identifying the cause of AKI and document the patient's clinical record. A complete history of fluid loss. It should record the results of previous serum creatinine and electrolytes, presence of comorbid conditions, history of urinary tract infections, history of surgery, radiological procedures, infections, and medication history. Symptoms may include a palpable bladder, enlarged prostate gland, vasculitis rash, uveitis, fever, or swelling and pain in joints. Physical examination should include an assessment of volume status, signs and symptoms of heart failure, embolism, infection, and sepsis [34].

Laboratory tests are required to diagnose AKI. Basic laboratory tests required include examination of urea levels, electrolytes, serum creatinine, serum bicarbonate, complete blood count, calcium, phosphate, inflammatory markers such as C-reactive protein (CRP), urinalysis, and if there is suspicion of infection, blood and urine cultures are performed. For suspected obstructions or suspected pyonephrosis, blood films, creatinine kinase, chest X-rays, and ultrasonography of the renal tract within 24 hours may also be considered. In cases where there is no precipitating cause of AKI, renal immunological examinations: such as serum electrophoresis, antinuclear antibodies (ANA), complement, immunoglobulins, anti-neutrophil cytoplasmic antibodies (ANCA), anti-glomerular basement membrane antibodies, and Bence Jones urine protein and biopsy renal failure may be required [34].

The presence of hematuria may refer to intrinsic renal damage. The presence of leukouria may refer to infection or autoimmunity. The presence of crystals may refer to drug-induced AKI. Renal imaging using ultrasonography can be used to help determine the reversible etiology of AKI such as the presence of obstructive kidney stones. A decrease in kidney size or echogenicity indicates CKD. Renal Doppler ultrasound can help identify ischemia and decreased renal blood flow. A high resistance index (>0.75) indicates decreased renal perfusion. Renal biopsy can be used in cases where ultrasound results are normal but the patient does not improve after 3-4 weeks when the intrinsic renal disease is suspected [30, 35].

Recognition of AKI currently relies on an increase in serum creatinine and/or a decrease in urine production, both of which are relatively poor biologic markers. Serum creatinine remains a nonspecific marker for AKI and does not indicate the site or severity of kidney damage. The rise in serum creatinine is delayed if associated with the onset of damage. In addition, urine production measurements are not routinely performed. Therefore, more specific biological markers in either serum or urine are currently being investigated. Researchers have examined several biological markers in small studies. It is including: neutrophil gelatinase-associated lipocalin (NGAL), interleukin-8 (IL-8), kidney injury molecule-1 (KIM-1), liver fatty acid binding protein (L-FABP) cell cycle arrest markers, insulin-like growth factor binding factor 7 (IGF BP-7), and tissue inhibitor of metalloproteinases 2 (TIMP2). More data in more specific studies are needed before these markers are recommended for routine use. It is not enough to use only one biological marker in the AKI diagnosis because the causes are heterogeneous. The thing to remember is that if there is an increase in serum creatinine an underlying cause must be sought [34, 35].

The pathophysiological mechanisms that explain the association between serum PCT and AKI remain unclear. Various inflammatory responses are thought to play a role in the AKI development [36, 37]. Various studies have confirmed that bacterial toxins and other mediators can trigger PCT release [13]. PCT acts as a chemoattractant in areas of inflammation. , and directly causes more monocytes to invade the inflammation

area. PCT is initially produced in adherent monocytes and then contributes to an increase in circulating PCT by attracting parenchymal cells as they attach directly to activated monocytes. High PCT levels eventually act as a direct chemoattractant to a greater number of monocytes and cause inflammation-mediated cell injury [38]. PCT mRNA expression by peripheral blood mononuclear cells is stimulated by LPS or other toxins released by microbes [38, 39].

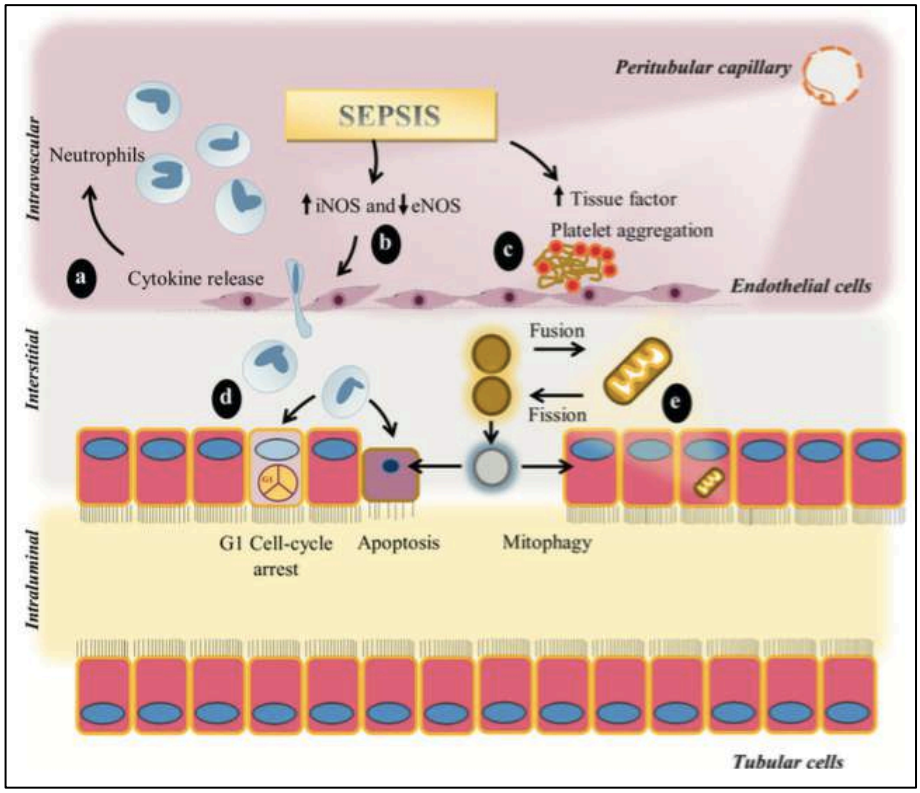

Figure 3. Pathophysiology of Sepsis-associated Acute Kidney Injury [40]

Additionally, PCT can also be produced due to an indirect pathway evoked through the host response through the release of inflammatory cytokines, such as IL-1β, IL-6, and TNF-α, which play a significant role in the development of AKI. In addition, there is another mechanism that the direct toxin effect of PCT on mesangial cells in the glomerulus exists. According to the study, PCT damages mesangial cells by causing them to produce more IL-6, iNOS, and TNF-α. Which resulted in damage to actin microfilaments and apoptosis in mesangial cells. In addition to cytotoxicity and inflammation effects, increased PCT has also been reported to be associated with increased creatinine and decreased GFR [14–16]

Sepsis causes changes in macrocirculation and microcirculation throughout the body. It was characterized by decreased peripheral vascular resistance, maldistribution of blood flow to tissues, and impaired perfusion. These changes lead to a significant decrease in capillary density. Furthermore, there is an increase in the heterogeneity of regional blood flow distribution in tissues (Fig. 3). Microcirculation changes like this are often dominated by reduced blood vessels with continuous flow. Which creates hypoperfusion and hypoxia [41, 42].

Platelets, fibrin, erythrocytes, and leukocytes together with damaged endothelial cells cause capillary occlusion. In addition, the increased permeability that occurs in sepsis causes interstitial edema and fluid retention, increasing the severity of sepsis and impairing oxygen diffusion to target cells. The result is impaired renal microcirculation perfusion that aggravates venous congestion. Endothelial cells damaged by the inflammatory response produce fewer vasodilators (eg nitric oxide/NO). Causing vasoconstriction and impairing blood flow. The vasoconstrictors, vasodilators, and oxidative stress at the endothelial level imbalance are thought to be important causes of AKI development in sepsis. Capillary occlusion due to the

interaction of leukocytes with activated endothelial cells, Vasoconstriction, and the coagulation system activation cause local compensation of microcirculatory flow and regional ischemia, thereby impairing renal function [41, 42].

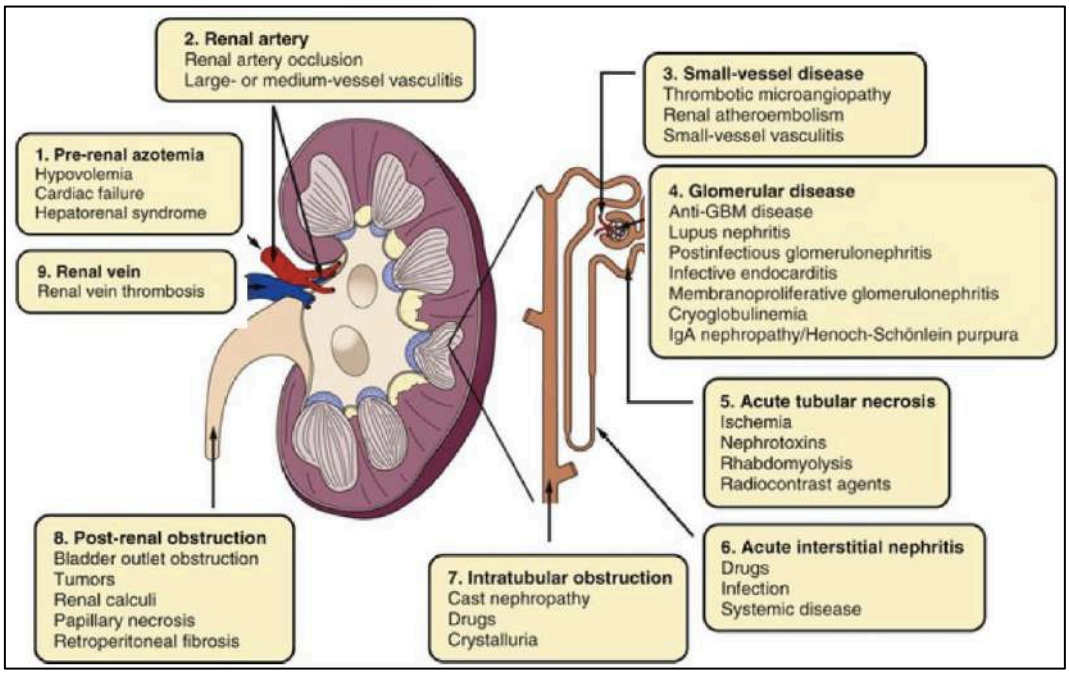

Figure 4. Etiology of Acute Kidney Injury [43]

Based on previous studies, sepsis AKI was considered a renal macrocirculation disorder resulting from ischemia, cell damage, and acute tubular necrosis. However, increasing evidence from other studies suggests that AKI can occur in hypoperfusion absence, even with normal or increased renal blood flow. It explains why hemodynamic correction often fails in septic AKI treatment [44].

As previously stated, acute kidney injury is a syndrome with a broad spectrum of etiologies. AKI can be divided into pre-renal, renal, and post-renal AKI based on the causative mechanism. The cause of pre-renal AKI is renal hypoperfusion due to hypovolemia. Or the decreased effective circulating volume. For example, sepsis and heart failure, and caused by intrarenal hemodynamic disturbances such as non-steroidal anti-inflammatory drugs usage. Renal AKI is caused by abnormalities in the vascular or tubular components of the kidney directly. For example, due to vasculitis, malignant hypertension, acute glomerular nephritis, interstitial nephritis, nephrotoxic substances, and so on that cause intrarenal vasoconstriction, ischemia, and decreased renal filtration rate. While post-renal AKI is usually caused by intrarenal and extra-renal obstruction problems that interfere with renal blood flow [45].

Despite many studies conducted over the last decade, the pathophysiology of acute kidney injury (AKI) caused by sepsis is still not fully understood. The AKI pathophysiology in sepsis is complex and multifactorial. It includes: intrarenal hemodynamic changes, endothelial dysfunction, inflammatory cell infiltration in the renal parenchyma, intraglomerular thrombosis, and tubular obstruction by necrotic cells and debris. Several recent studies have revealed three main components in the pathophysiology of AKI sepsis, including inflammation, microcirculatory flow abnormalities, and the adaptive response of cells to tissue changes and injury [41, 42].

There is an association between inflammatory mediators of pathogenic origin and an activated immune system (e.g. lipopolysaccharides, cytokines, damage-associated molecular pattern molecules (DAMPs)/pathogen-associated molecular patterns (PAMPs) and the development of septic AKI. The fact that the kidneys receive 20% of cardiac output exists) and filter about 120 to 150 ml of plasma every minute, leaving the kidney as the leading organ potentially exposed to these mediators [42, 46].

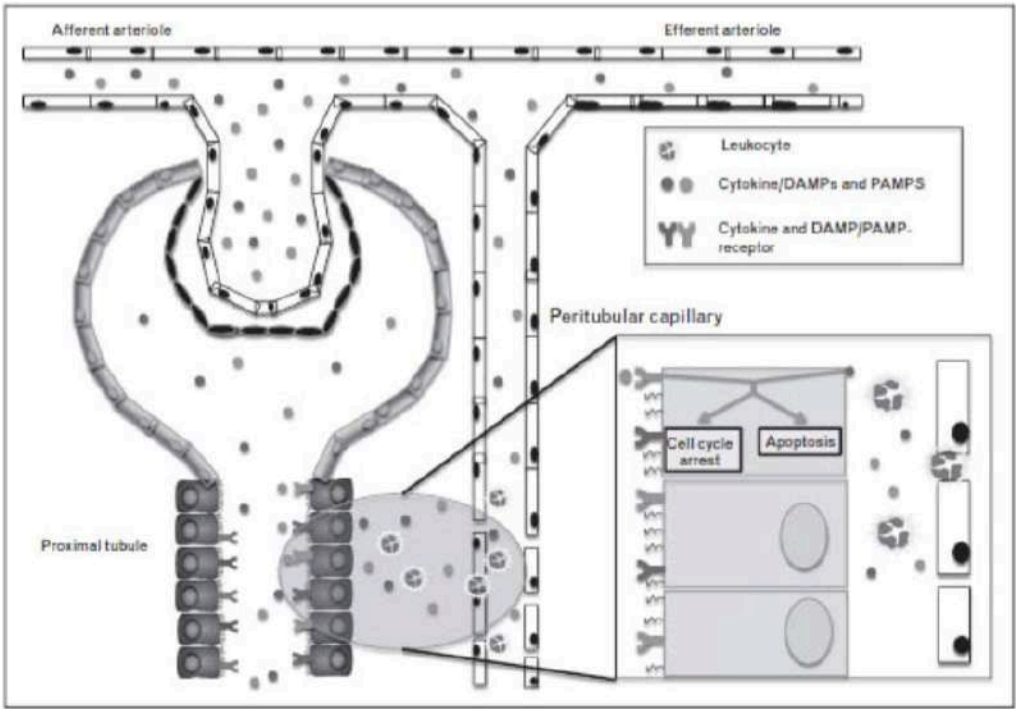

Figure 5. During sepsis, DAMPs, PAMPs, and proinflammatory cytokines have the potential to injure tubular cells from the tubular and interstitial sides [42]

During sepsis, infection triggers a host response that activates immune system mechanisms to fight infection and restore tissue injury. DAMPs and PAMPs can be recognized, not only by immune cells but also by epithelial and parenchymal cells, through interactions with receptors. Including Toll-Like Receptors (TLR), C-type lectin receptors, retinoic acid-inducible gene 1-like receptors, and nucleotide-binding oligomerization domain-like receptors. The involvement of these receptors results in the upregulation of inflammatory gene transcription and the innate immune system. Leading to the release of cytokines as proinflammatory mediators. These cytokines produced in large quantities during the early phase of sepsis activate leukocytes, endothelial cells, and epithelial cells, leading to leukocyte and platelet activation, microvascular dysfunction, hypoxia, and tissue damage [42, 46].

Proinflammatory mediators activate endothelial cells and increase vascular permeability. Active endothelial cells increase the expression of adhesion molecules and release additional pro-inflammatory mediators that release substances and enzymes that damage tissue, further aggravating inflammation. Leukocytes in the bloodstream can directly activate tubular epithelial cells by releasing proinflammatory mediators, damage-associated molecular pattern molecules (DAMPs), and pathogen-associated molecular patterns (PAMPs). It is through the peritubular microcirculation or filtered into the glomerulus. It then enters the proximal tubule and binding with TLR2 and TLR4, which causes changes in the metabolic and functional state of tubular epithelial cells, producing oxidative stress and causing damage to the renal tubules (Fig. 6) [42, 46].

Endothelial cells and renal tubules that are exposed to inflammatory reactions and cause dysfunction in microcirculation flow have an adaptive response to changes in the surrounding environment. Endothelial cells and renal tubules as the main targets in septic AKI are highly susceptible to mitochondrial damage and oxidative stress [44, 47].

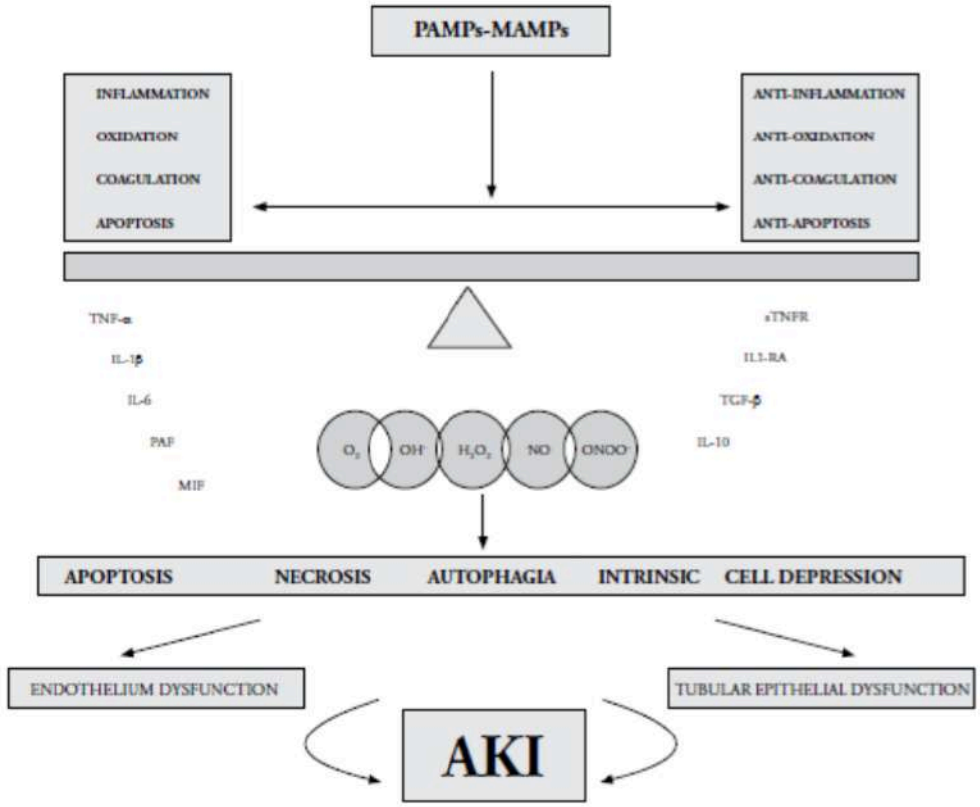

Figure 6. Adaptive Response of Endothelial Cells and Renal Tubules to Local Changes Due to Sepsis

Oxidative stress caused by substances or enzymes stimulated by inflammatory mediators can induce apoptosis of endothelial cells and renal tubules. Other adaptive responses to reduce inflammation include: energy starvation due to organelle autolysis (autophagy), mitochondrial digestion and dysfunction (mitophagy), and cell cycle arrest. How this process occurs is still not fully understood. Even though this adaptive response aims to reduce exposure to inflammatory reactions and save healthy cells from damage, if it is excessive it will cause massive cell death, leaving areas of necrosis and causing organ damage [44, 47].

CONCLUSION

PCT acts as a chemoattractant in the inflammation area and causes more monocytes to invade the inflammation. PCT is initially produced in adherent monocytes and then contributes to an increase in circulating PCT by attracting parenchymal cells as they attach directly to activated monocytes. High PCT levels ultimately act as a direct chemoattractant to monocyte counts.

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