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Carbamylated haemoglobin as a marker for predicting progression of renal failure

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Abstract Renal failure occurs when one or both kidneys are unable to function properly. It can be classified into two types: acute and chronic. Acute renal failure is a sudden and temporary condition, while chronic renal failure develops gradually and can lead to permanent kidney damage. Acute kidney injury arises when the kidneys lose their ability to filter waste from the bloodstream effectively. This can result in the accumulation of harmful waste products and an imbalance in the blood's chemical composition. Previously, acute renal failure was referred to as acute kidney injury. Hospitalized patients, particularly those requiring critical care, are at a higher risk of developing acute kidney injury. Chronic kidney disease (CKD), also referred to as chronic kidney failure, is characterized by a persistent decline in renal function. The kidneys play a vital role in filtering waste products and excess fluid from the blood to produce urine. In severe cases of chronic kidney disease, the body accumulates harmful levels of fluids, electrolytes, and waste products. While creatinine, urea, uric acid, and electrolytes are commonly analyzed as markers of kidney function, numerous studies have highlighted and validated the importance of alternative markers such as cystatin C and β-Trace Protein. Isocyanic acid reacts with the amino groups in haemoglobin to form Carbamylated Haemoglobin (CarHb). In the body, isocyanic acid is produced as a byproduct of urea dissociation. Patients with renal failure exhibit higher levels of Carbamylated Haemoglobin compared to healthy individuals. Furthermore, CarHb levels are lower in patients with acute kidney injury (AKI) than in those with chronic kidney disease (CKD). This indicates that as kidney disease progresses from an acute to a chronic stage, Carbamylated Haemoglobin levels increase. Therefore, Carbamylated Haemoglobin can serve as a potential marker for predicting the progression of renal failure.

Keywords: carbamylated haemoglobin, renal failure, chronic kidney disease

1. Introduction

Renal failure occurs when the kidneys lose their ability to function properly. Acute renal failure is typically a sudden and temporary condition, whereas chronic kidney disease gradually worsens over time (Star & Robert, 1998). Acute renal failure involves a rapid decline in kidney function, occurring within a few hours or days. As noted by Biesen et al. (2006), it may result from factors such as infection, severe dehydration, poisoning, or adverse drug reactions. In most cases, kidney function gradually improves over several days. However, acute renal failure can sometimes lead to chronic kidney disease, causing irreversible damage. Chronic kidney disease (CKD) is diagnosed by a glomerular filtration rate (GFR) of less than 60 mL/min per 1.73 m^2, evidence of kidney damage, or both, persisting for at least three months, regardless of the underlying cause. Over time, the classification and terminology associated with CKD have evolved.

Chronic kidney disease (CKD) is primarily caused by diabetes and hypertension in high- and middle-income countries, as well as in many low-income countries (Webster et al., 2017). The experience of kidney disease and renal failure varies significantly from person to person. Symptoms indicating potential kidney dysfunction include severe weakness or fatigue, nausea and vomiting, confusion or difficulty concentrating, swelling (edema), particularly in the face, hands, or ankles, increased urination, muscle cramps or spasms, dry or itchy skin, loss of appetite, and a persistent unpleasant taste (Abdel-Kader & Khaled, 2022).

One of the key pathophysiological mechanisms contributing to the inflammatory state in chronic kidney disease (CKD) is a maladaptive cellular response to injury. This response activates proinflammatory and profibrotic signaling pathways over an extended period. The systemic and chronic proinflammatory conditions resulting from CKD dysfunction promote vascular and myocardial remodeling, leading to atherosclerotic lesions, vascular calcification, vascular senescence, myocardial fibrosis, and heart valve calcification (Lameire & Norbert, 2005). The stage of CKD is determined by the glomerular filtration rate (GFR), which reflects the degree of renal function:Stage 1: Kidney damage with a normal or elevated GFR ,Stage 2: Mild decline in GFR, Stage 3a: moderate decline in GFR, Stage 3b: Furtherdecline in GFR,Stage 4: Significantly decline in GFR Stage 5: Kidney failure is defined as a GFR of less than 15 mL/min/1.73 m2 or the need for dialysis (Mehta et al., 2003).

Carbamylated haemoglobin (CarHb) is formed when isocyanate interacts with the N-terminal valine residues of the α and β chains of haemoglobin. It is found in higher concentrations in patients with renal failure (Wynckel et al., 2000). Under normal conditions, isocyanate levels are approximately 1% of urea levels (Stark et al., 1960). In renal failure, urea and other metabolites are retained, providing an indication of nitrogen buildup in the body. Under physiological conditions, urea quickly breaks down to produce cyanate and ammonia (Dirnhuber & Schutz, 1948). Protein carbamylation occurs as a result of interactions between protonated cyanate, isocyanic acid, and the amino groups of proteins (Lee & Manning, 1973). Studies have shown that haemoglobin, plasma proteins, leukocyte proteins, and amino acids undergo carbamylation in renal failure (Fluckiger et al., 1981). The production of carbamylated haemoglobin (CarHb) is attributed to the unique reactivity of haemoglobin's N-terminal valine with isocyanate (Ensen et al., 1973).

Numerous studies have shown that the pharmacologic carbamylation of hemoglobin by cyanate involves binding to an anion before proton movement leads to carbamylation, affecting residues such as Val-1 and Arg-141 on the α chain (Nigen et al., 1976). Hemoglobin's A chains carbamylate twice as quickly in the deoxy state as they do in the oxy state. Additionally, it has been observed that carbamylation of hemoglobin S enhances oxygen delivery and inhibits sickling (Cerami & Manning, 1971). These findings suggest that the structural changes caused by the carbamylation of individual hemoglobin chains influence its metabolic functions. The acid hydrolysis of CarHb converts the modified N-terminal valine into valine hydantoin. High-performance liquid chromatography (HPLC) or gas chromatography are typically used to quantify CarHb levels (Manning et al., 1973). In patients with renal failure, particularly those undergoing dialysis or receiving a kidney transplant, blood urea nitrogen (BUN) and CarHb levels are closely correlated (Kwan et al., 1991).

However, the kinetics of haemoglobin carbamylation in this context remain unknown. The relationship between the rate of urea accumulation and increasing urea concentrations over time is particularly intriguing. Additionally, it remains unclear whether variations in phosphate and bicarbonate levels associated with renal failure could influence haemoglobin carbamylation. Studies have shown that many plasma proteins and amino acids undergo carbamylation in patients with chronic renal failure, with carbamylated haemoglobin being the most extensively studied carbamylated protein (Kraus et al., 1985). Several studies have indicated that the levels of carbamylated haemoglobin are influenced by the severity and duration of renal failure, with patients experiencing chronic renal failure having higher levels than those with acute renal failure. Similarly, as renal function improves following a successful renal transplant, carbamylated haemoglobin levels decrease (Mith et al., 1988).

2. Review

Renal failure has affected numerous generations over many years. In its critical stages, various symptoms and signs become apparent, yet many people remain unaware of them. In a healthy individual, the symptoms are initially subtle and may go unnoticed as they progress, though they can be more pronounced in patients with multiple comorbidities. Therefore, to assess the severity and progression of renal failure, an effective marker is essential. While there are several indicators used to evaluate renal failure, carbamylated hemoglobin stands out as one of the most promising markers for tracking the progression of the condition.

Numerous studies suggest that carbamylated hemoglobin could be a valuable marker for tracking the progression of renal failure, although some studies challenge this conclusion. Research by Andrew Davenport indicates that carbamylated hemoglobin may serve as a useful marker for patients undergoing hemodialysis in cases of end-stage renal failure (Davenport et al., 1996). Similarly, James Stim's research suggests that carbamylated hemoglobin has potential as a measure of chronic urea exposure in renal failure, as its formation rate is influenced by both the average blood urea concentration and the duration of urea exposure (Stim et al., 1995). Additionally, Oimomi et al. (1986) found that carbamylated plasma proteins are elevated in renal failure, making them a potential marker for the condition.

Carbamylated hemoglobin has been proposed as a potential indicator of chronic renal failure, as suggested by Smith's research (Smith et al., 1988). In hemodialysis patients, a study by Balion found that both carbamylated hemoglobin and carbamylated plasma proteins are useful in assessing the patient's uremic condition (Balion et al., 1998). According to Jin Suk Han, the in vivo process of hemoglobin carbamylation progresses during the uremic phase. In more advanced stages of chronic renal failure (CRF), some irreversible carbamylated hemoglobin may be present (Jin Suk Han et al., 1997). Wynckel's research (Wynckel et al., 2000) suggests that CarHb measurement is particularly useful in cases of acute renal failure (ARF) when there is no known history of renal disease. Additionally, Tarif et al. (1997) found that CarHb could provide a more accurate measure of uremia control, as it reflects changes in dialysis blood urea nitrogen levels.

Carbamylated hemoglobin has been proposed as a therapeutic marker for hemodialysis, according to a study by Y. Hasuike (Hasuike et al., 2002). Tasanarong suggested that carbamylated hemoglobin levels could serve as a reliable, non-invasive method for differentiating between acute renal failure and chronic renal failure, based on his 2002 research (Tasanarong et al., 2002). In addition to hemoglobin, Kalim's findings indicate that carbamylation of other plasma proteins, such as albumin, may help predict the progression to end-stage renal disease (Kalim et al., 2013). Tang et al. (2023) observed that carbamylation and anemia alter the relationship between HbA1c levels and the progression of chronic kidney disease (CKD) in patients with both diabetes and CKD. Drechsler's research revealed that protein carbamylation is associated with heart

failure and mortality in diabetic patients with end-stage renal disease (Drechsler et al., 2015). Koeth concluded in his study that protein carbamylation predicts mortality in end-stage renal disease (Koeth et al., 2013).

Uremia results from abnormal nonenzymatic glycosylation of proteins, a process unrelated to carbamylation, as noted in a study by Sabater. This condition can be partially corrected through hemodialysis (Sabater et al., 1991). Berg et al. (2013) found that serum carbamylated albumin may serve as a risk factor for mortality in patients with end-stage renal disease. Another study by Gorisse suggests that carbamylated proteins may worsen the progression of chronic kidney disease (Gorisse et al., 2022). Imamura's research indicates that carbamylated erythropoietin protects the kidneys against ischemia-reperfusion injury by promoting angiogenesis (Imamura et al., 2008). Tahora's study proposes that carbamylated haemoglobin (CarHb) could be a promising biomarker for the early diagnosis of chronic kidney disease (Tahora et al., 2021). Research by Abdelwhab suggests that carbamylated haemoglobin levels may be used to assess the effectiveness of hemodialysate (Abdelwhab & Ahmed et al., 2008). Additionally, Keshava's study indicates that carbamylated haemoglobin is a useful marker for distinguishing between acute renal injury and chronic kidney disease (Keshava et al., 2024). Naresh's research reached similar conclusions (Naresh et al., 2018). However, Frazao concluded that carbamylated haemoglobin is ineffective for differentiating between moderate acute renal failure and prerenal azotemia (Frazao et al., 1995).

2.1. Acute renal failure

Acute renal failure refers to the rapid decline in kidney function, occurring within less than two days, which impairs the kidneys' ability to eliminate waste and maintain proper fluid and electrolyte balance in the body. Common causes include conditions such as placental abruption, placenta previa, burns, dehydration, septic shock, pyelonephritis, septicemia, acute tubular necrosis, and urinary tract obstruction, among others. Symptoms typically include pain in the lower abdomen, burning sensation during urination, nausea, vomiting, shortness of breath, blood in the urine, and generalized swelling of the body (Kellum et al., 2021).

2.2. Chronic renal failure

The term chronic kidney disease (CKD), previously referred to as chronic renal failure (CRF), encompasses a spectrum of reduced kidney function, ranging from at-risk or damaged kidneys to mild, moderate, and severe chronic kidney failure. CKD is a significant global public health concern (Vaidya & Aeddula et al., 2022). It can result from various underlying conditions, including heart disease, heart failure, diabetes, hypertension (high blood pressure), obesity, glomerulonephritis, IgA nephropathy (IgAN), HIV-associated nephropathy, polycystic kidney disease, autoimmune diseases such as lupus (lupus nephritis), sepsis, hemolytic uremic syndrome (HUS), kidney cancer, and kidney stones, among others (Evans & Taal et al., 2015). Individuals with CRF may exhibit symptoms such as anemia, high blood pressure, swelling (edema) in the hands, ankles, and feet, fatigue, reduced urine output, blood in the urine, dark-colored urine, and shortness of breath (Almutary et al., 2013). Table 1 provides a comparison between acute and chronic renal failure.

Table 1 Contrast between acute and chronic renal failure.

Acute Kidney Failure	Chronic Kidney Failure
typically caused by a drug, illness, or injury	typically caused by a chronic illness
Kidney function quickly deteriorates.	Kidney function eventually deteriorates.
The symptoms might appear suddenly and can be quite serious.	Symptoms might not show up until the damage is severe.
Addressing the root cause is the aim of the treatment.	Managing the underlying issue is the aim of the treatment.
frequently reversible with timely care.	Irreversible, with a focus on stopping further deterioration.

3. Markers of Renal Failure

3.1. Creatinine

Creatinine is a byproduct of the breakdown of muscle creatine phosphate. The creatinine clearance test is commonly used to assess and monitor the progression of renal disease. Elevated blood creatinine levels beyond the normal range serve as key indicators of renal failure. As noted by Waitar et al. (2009), creatinine is one of the most reliable markers of renal impairment because it is neither secreted nor reabsorbed by the renal tubules and is not influenced by dietary intake.

3.2. Urea

Urea, a nitrogenous byproduct of protein metabolism, is composed of a two-atom nitrogen molecule and is readily filtered by the kidneys. Of the urea that is digested, 40–70% can be reabsorbed into the plasma through the tubular epithelium. Factors influencing blood urea levels include the rate of hepatic urea production, dietary protein intake, the extent of tubular reabsorption, the use of certain medications, and the presence of gastrointestinal bleeding. While urea demonstrates high

sensitivity, its low specificity limits its diagnostic precision, although it remains an easily interpretable and measurable marker for renal disease detection (Al-Hazmi et al., 2020).

3.3. Cystatin -C

Cystatin C (Cys C), a 13-kDa protein that acts as a cysteine proteinase inhibitor, is the latest biomarker used to quantify and classify the stages of chronic kidney disease. Cys C offers certain advantages over creatinine in therapeutic applications, as it is produced by all nucleated cells and its serum levels remain unaffected by age or muscle mass. Since Cys C is efficiently filtered by the kidney's glomerular membrane and promptly reabsorbed in the proximal tubule (PT), where it undergoes catabolism, it typically does not appear in urine or re-enter the bloodstream (Deventer et al., 2011).

3.4. Glomerular filtration rate (GFR)

The glomerular filtration rate (GFR) represents the combined filtration rates of the kidney's functional nephrons. GFR is considered the most reliable indicator of kidney function when assessed alongside albuminuria, and it is crucial in determining the severity of chronic renal disease in an individual (Soveri et al., 2014). A normal GFR, typically around 120 ml/min/1.73 m^2 in young adults, decreases with age in healthy individuals and is influenced by factors such as age, sex, and body size. Since a decline in GFR can signal renal disease before the onset of kidney failure, a consistently low GFR serves as a key diagnostic criterion for chronic kidney disease (CKD) (Florkowski & Chew-Harris et al., 2011).

3.5. Kidney injury molecule-1

Kidney Injury Molecule-1 (KIM-1) plays a crucial role in promoting epithelial phagocytosis in the injured kidney, converting proximal epithelial cells into phagocytes. This process may have significant pathophysiological implications for modulating immune responses and facilitating post-injury repair. According to Bonventre and Yang et al. (2010), KIM-1 is a highly sensitive and specific urinary biomarker for kidney dysfunction and could serve as a potential therapeutic target for various renal disorders.

3.6. Neutrophil gelatinase-associated lipocalin (NGAL)

Neutrophil gelatinase–associated lipocalin (NGAL), a protein belonging to the lipocalin superfamily, was initially identified in active neutrophils and is believed to have intrinsic antibacterial properties. However, it was later discovered that NGAL is also released by various other cell types, including those in the renal tubules, in response to different forms of trauma (Bolignano et al., 2008). The role of NGAL is being studied in relation to numerous clinical conditions that may lead to acute kidney injury or chronic kidney disease (CKD), such as lupus nephritis, glomerulonephritis, obstructions, dysplasia, polycystic kidney disease, and IgA nephropathy (Devarajan, 2008).

3.7. Beta-2 microglobulin

Beta-2 microglobulin (B2M) is a protein present on the surface of most cells in the body. It forms part of the MHC class I molecules, which are found in all nucleated cells (Bethea & Forman, 1990). The renal proximal tubules, responsible for reabsorbing water, proteins, vitamins, minerals, and other essential substances, reabsorb B2M after it passes through the glomeruli, the blood-filtering units. Although B2M is normally found in trace amounts in urine, its concentration increases when the renal tubules are damaged or diseased, as the protein's reabsorption capacity is reduced. Additionally, if the glomeruli are injured and unable to filter B2M, blood levels of the protein rise (Miyata et al., 1998).

3.8. Electrolyte

The electrolyte test is used to diagnose and manage a range of conditions, including renal, endocrine, acid-base, and water balance disorders, by measuring sodium, potassium, chloride, and bicarbonate levels. Potassium is one of the most reliable electrolyte markers for renal failure (Langston, 2008). During renal failure, reduced potassium synthesis in the distal tubule, combined with impaired filtration, results in elevated plasma potassium levels. According to Dhondup and Qian (2017), hyperkalemia is the most dangerous and potentially life-threatening complication of renal failure.

3.9. Carbamylated haemoglobin as a marker for renal failure

Carbamylated hemoglobin is formed when hemoglobin interacts with blood urea, leading to the addition of carbamyl groups. This process is particularly important in cases of renal failure, as the kidneys normally eliminate urea from the bloodstream. In individuals with renal failure, elevated urea levels can result in higher concentrations of carbamylated hemoglobin (Mashahit et al., 2023). Figure 1 illustrates carbamylated hemoglobin as a marker for renal failure.

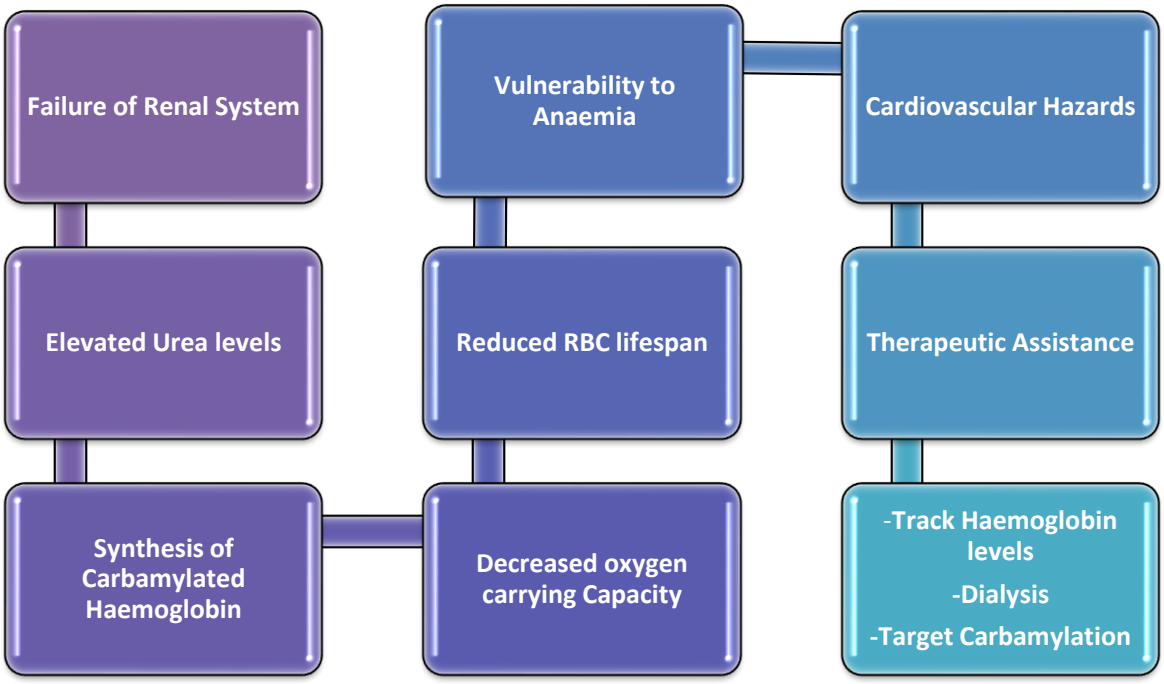

Figure 1 Carbamylated Haemoglobin as a marker of Renal Failure.

4. Conclusion

The measurement of carbamylated hemoglobin is a potential biomarker for assessing the severity of renal failure. Elevated levels of carbamylated hemoglobin may offer valuable insights into chronic kidney disease (CKD) and its associated complications, including cardiovascular issues, as these levels have been linked to poorer outcomes in CKD patients. While carbamylated hemoglobin is not widely used in clinical practice, ongoing research explores its potential role in evaluating renal function and related health concerns in individuals with kidney disease. Therefore, it can be considered a promising biomarker for predicting the progression of renal disease.

Ethical Cconsiderations

Not applicable.

Conflict of Interest

The authors declare no conflicts of interest.

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