Role of B2-Microglobulin as A Marker for Acute Kidney Injury in Patients with Intracerebral Hemorrhage in Medical Intensive Care Unit: An Overview

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Abstract

The ability of the human immune system to discriminate between self and nonself molecules is one of its key roles. Class I antigens, which aid the immune system in recognizing self-molecules, are present in the majority of nucleated cells in the human body. There is a light chain that goes along with the heavy chain in these antigens. This light-protein chain is known as β2-microglobulin, and it can be excreted into serum. Midway through the 1960s, β2-microglobulin (β2M) was identified as a urine protein in the urine of patients suffering from cadmium poisoning or Wilson's disease. Primarily, glomerular filtration is used to remove β2M from serum; however, the proximal convoluted tubule reabsorbs and catabolizes over 99.9% of the filtered protein, leaving urine with a low β2M concentration (often less than 360 μg/l). Megalin–cubilin complex is thought to be the mechanism of β2M removal from the tubular fluid based on ligand blotting experiments, megalin animal knockouts, and human illness. Due to mutations in the LRP2 megalin gene, this condition is linked to developmental delay, tubular proteinuria, and multisystemic disorders. We came to the conclusion that, when patients in the intensive care unit (ICU) have intracerebral haemorrhage (ICH), B2-MG can be used as a predictive marker of the onset of AKI. highlighting the most recent guidelines for the diagnosis and treatment of these patients while taking into account the evaluation of β2-MG as a tool to achieve early detection of AKI in individuals with ICH. More research is required to fully examine this problem.

Key words: β2-microglobulin; AKI; ICU; Kidney.

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Aim of work:

To evaluate β2-microglobulin as a marker of acute kidney injury (AKI).

Intracerebral hemorrhage: a great concern

A deadly form of stroke known as intracerebral haemorrhage (ICH) occurs when a hematoma forms within the brain parenchyma, either with or without blood extending into the ventricles. It is the deadliest type of stroke; it accounts for 10% to 15% of all strokes, has a significant morbidity rate, and has a one-year death rate above 50% [1]. There are two primary types of strokes: ischemic and hemorrhagic. Reduced blood flow causes neuronal infarction and insufficient oxygenation of the brain parenchyma in ischemic stroke. Most frequently, vascular damage that results in hematoma formation and a local mass effect on the surrounding brain tissue causes hemorrhagic stroke [2].

A variety of diseases with varying natural histories, workups, and management approaches comprise ICH. ICH is classified as main or secondary based on the cause. Cerebral amyloid angiopathy (CAA) and hypertensive haemorrhage are the two main disorders that make up primary ICH, which has a greater incidence. Over 80% of ICH cases are caused by these two factors combined, with hypertensive haemorrhage being involved in roughly 55% of ICH cases overall [2]. The common sites of the bleed are the basal ganglia (50%), cerebral lobes (10% to 20%), the thalamus (15%), pons and the brain stem (10% to 20%), and the cerebellum (10%) (Figure 1) [1].

Small arteries and arterioles develop lipohyalinosis as a result of persistent hypertension. Atheromas are formed when hyaline, collagen, protein, and fat thin the adventitia and replace arterial smooth muscle. Small patches of brain ischemia are caused by the stiffened and constricted lumen, which is followed by lacunes-related encephalomalacia. This term is derived from the Latin word “lacunae,” which appropriately means “lake” [2]. Patients with persistent hypertension face a 2% annual risk of bleeding due to weakening of the tunica media at vascular bifurcations, in addition

to an increased risk of ischemic events. Moreover, the impaired muscle layer cannot respond to local haemorrhage by vasoconstricting, which perpetuates bleeding and advances ICH. It was often believed that weakening of the artery walls created "Charcot–Bouchard microaneurysms," which burst and cause bleeding. Nevertheless, subsequent research using electron microscopy has demonstrated that these so-called "microaneurysms" are actually tiny hematomas found in the extravascular or subadventitial regions [2].

Acute kidney injury (AKI): the dilemma of the current era

The complicated illness known as acute kidney injury (AKI) is typified by an abrupt decline in renal function that may have multiple underlying causes and is linked to intricate pathophysiological processes. With a frequency ranging from 5.0% to 7.5% in hospitalised patients and up to 50–60% in critically ill patients, AKI is a common diagnosis [3]. AKI has long-term effects, including increased risks of cardiovascular events, the development of chronic kidney disease (CKD), and long-term mortality. It is also linked to longer hospital stays, higher healthcare expenses, and in-hospital mortality [4]. Acute Kidney Injury Network (AKIN) proposed the term "AKI" to better capture the spectrum of acute renal failure (ARF), which was previously known as "acute renal failure" (ARF). The severity of ARF can vary, ranging from asymptomatic changes in laboratory parameters to life-threatening disorders of volume regulation, electrolytes, and acid-base composition of the plasma [5].

Pre-renal acute kidney injury (AKI), acute tubular necrosis, acute interstitial nephritis, acute glomerular disorders, and acute obstructive nephropathy are some of the pathophysiological mechanisms that contribute to AKI, a complicated condition [6]. These causes can be divided into three categories: prerenal AKI (resulting from functional adaptation to hypoperfusion of structurally normal kidneys; up to 60% of cases); intrinsic renal AKI (resulting from structural damage to any part of the renal parenchyma; up to 40% of cases); and, less frequently, postrenal AKI (resulting from urinary tract obstruction) [7]. Because the kidneys are extremely susceptible to any kind of systemic disturbance, the majority of causes of AKI are actually not specific to the kidneys. In fact, this fact is highlighted by the fact that the most frequent causes include hypovolemia, cardiogenic shock, septic shock, and post-major surgery [8].

The basic function of the kidneys is to maintain homeostasis; loss of kidney excretory function indicates issues with this function, such as the excretion of waste products from metabolism. As indicators of reduced kidney function, serum creatinine and urea nitrogen levels are frequently considered more important than the excretory function of the kidneys [6]. Fluid retention, which disrupts fluid balance and shows as peripheral edoema, third-space effusions, and pulmonary congestion, especially in heart failure patients, is caused by declining glomerular filtration rate (GFR) and activation of the renin-angiotensin system. In addition, as urine output regulates potassium excretion, hyperkalemia is a common adverse outcome of severe AKI [9].

When hyperkalemia-related anomalies appear on an ECG, it is deemed an emergency that has to be treated right away. Hyponatremia and hypernatremia can both occur when the kidney is unable to concentrate, or dilute urine as needed. Impaired phosphate clearance is the cause of hyperphosphataemia [6]. Importantly, kidney failure affects most organ systems of the body (Figure 2). The intestinal microbiota is the source of many uremic toxins associated with AKI, including p-cresyl sulphate and indoxyl sulphate. Due to AKI and the associated acidosis, azotaemia, intestinal ischaemia, and other changes in the intestinal microenvironments, the microbiota itself experiences changes in its composition. These changes have an impact on the microbiota's secretome and metabolites necessary for normal human physiology [10].

β2-microglobulin: the emerging biomarker of hope

The ability of the human immune system to discriminate between self and nonself molecules is one of its key roles. Class I antigens, which aid the immune system in recognising self-molecules, are present in the majority of nucleated cells in the human body. There is a light chain that goes along with the heavy chain in these antigens. This light-protein chain is known as β2-microglobulin, and it can be excreted into serum [11]. Midway through the 1960s, β2-microglobulin (β2M) was identified as a urine protein in the urine of patients suffering from cadmium poisoning or Wilson's disease. The β2-microglobulin protein in humans is encoded by the B2M gene, which is located on chromosome 15. There is no human genetic variation of β2M identified [12]. Small protein (11,800 Dalton), β2-microglobulin (β2M) is present in almost all nucleated cells (not red blood cells) and most bodily fluids, such as urine, synovial fluid, and serum. Furthermore, it seems to play a role on the cell surface as a component of the HLA complex [13].

The secondary structure of β2M consists of seven β-strands (Figure 3) which are organized into two β-sheets linked by a single disulfide bridge, presenting a classical β-sandwich typical of the immunoglobulin (Ig) domain [14]. Lacking a transmembrane region, β2M possesses a unique structural structure known as a constant-1 Ig superfamily domain, which it shares with other adaptive immune molecules such as class I and class II major histocompatibility complexes. For the

proper structural fold and function of β2M, two evolutionary conserved tryptophan (Trp) residues are crucial [15]. Trp60, which is exposed to the solvent at the peak of a protein loop, is essential in promoting the binding of β2M to MHC I. A unique modification to β2M's ability to self-aggregate into amyloid fibrils is caused by the Trp60 mutation, which weakens its contact with the heavy chain of MHC I in the structure of β2M, increases its stabilisation, and inhibits its amyloidogenic propensity. In vitro under physiological settings, β2M displays thermodynamic instability and becomes significantly fibrillogenic when the aspartate residue is replaced with the asparagine residue at position 76 [16]. Although β2M is expressed continuously in many cells, IFN-α would promote the production of β2M. β2M can regulate the expression of growth factors and hormones, induce the production of interleukin 6 (IL-6), 8, and 10 in different cell types, and oversee the interaction between cytokines and their receptors [17].

Similar to a classic oncogenic factor, β2M can promote the development and spread of several types of cancer. β2M facilitates the continued synthesis and deposition of bone-like proteins by cancer cells during bone metastases. Exogenous overexpression of β2M would facilitate the development and migration of mesenchymal stem cells by increasing the phosphorylation of cAMP response element-binding protein and upregulating IL-6 and vascular endothelial growth factor [18]. By inducing the epithelial to mesenchymal transition, β2M may facilitate deadly bone and soft tissue metastases. Additionally, β2M functions as a factor that induces apoptosis in a number of leukemic, lymphoma, and myeloma cell lines. In prostate cancer cells, inhibition of β2M increased radiation sensitivity by causing iron overload [19]. In patients receiving long-term hemodialysis, a high concentration of serum β2M causes β2M to accumulate in skeletal joints and create amyloid plaques. While there are various derivatives of β2M, full-length β2M makes up the majority of the fibrils. Furthermore, the fibril production lag period is twice as long when the β2M point mutation H51A is present [20].

Urinary β2M for the assessment of tubular function:

Primarily, glomerular filtration is used to remove β2M from serum; however, the proximal convoluted tubule reabsorbs and catabolizes over 99.9% of the filtered protein, leaving urine with a low β2M concentration (often less than 360 μg/l) [21]. Megalin–cubilin complex is thought to be the mechanism of β2M removal from the tubular fluid based on ligand blotting experiments, megalin animal knockouts, and human illness. Due to mutations in the LRP2 megalin gene, this condition is linked to developmental delay, tubular proteinuria, and multisystemic disorders [22].

Given human cubilin mutations, this interaction might be mediated by the megalin component of the megalin–cubilin complex. Proteins that are endocytosed by the megalin/cubilin complex are directed towards the endosomes, where acidification causes ligands to be released from their receptors [23]. It is uncertain how much β2M is recycled to the membrane surface with other MHC, broken down in lysosomes, or transported to the basolateral surface where it is bound by thyroglobulin or retinol binding protein. Since β2M is localised to the lysosomes, degradation appears to be the most likely destiny for this protein, according to findings from rat trials [24]. Contradictory evidence, however, points to the presence of convergent basolateral and apical endocytic systems in the proximal tubule. Since human proximal epithelial cells can transcytose the FcRn-β2M-IgG, part of the reabsorbed urine β2M may do so [25].

To the best of our knowledge, no studies have specifically looked into the transcytosis of β2M absorbed by the megalin pathway. Experiments carried some forty years ago provide some evidence for competitive suppression of the absorptive tubular mechanism between β2M and other proteins in the tubular fluid. More recent tests support the notion that a single mechanism mediates this process by suggesting similar transport kinetics [26]. As a result, when glomerular proteinuria is present, different levels of β2M excretion in the urine are possible. The handling of β2M in the tubules matures during the neonatal stage. Urinary β2M excretion peaks around the fifth day of life and subsequently drops to an adult level by three months of age. This characteristic implies that urinary β2M may have an age-dependent performance in addition to being a potentially accurate biomarker of tubular toxicity [27].

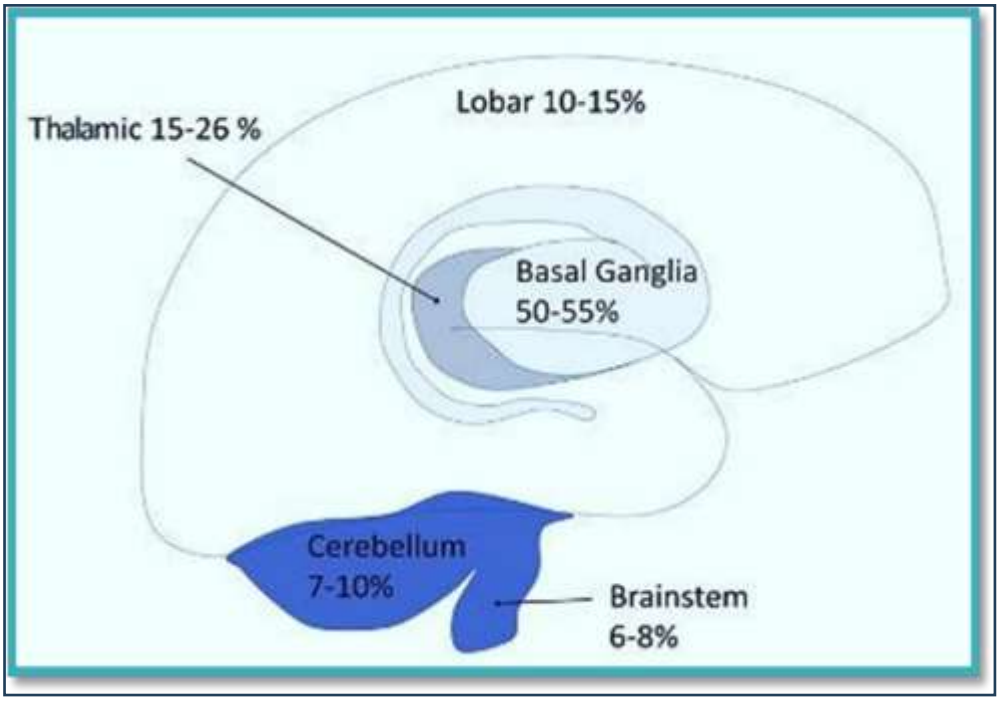

Figure (1): Anatomic distribution of intracerebral hemorrhage [2].

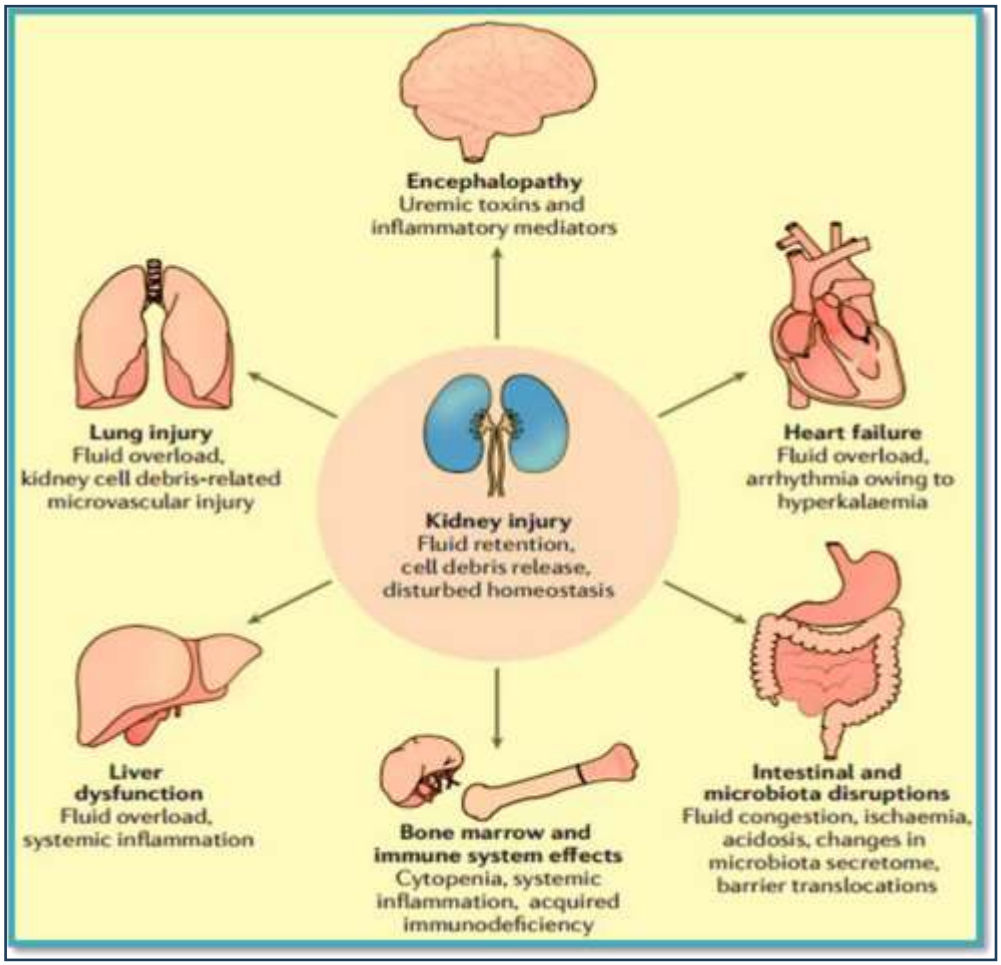

Figure (2): Systemic consequences of AKI.

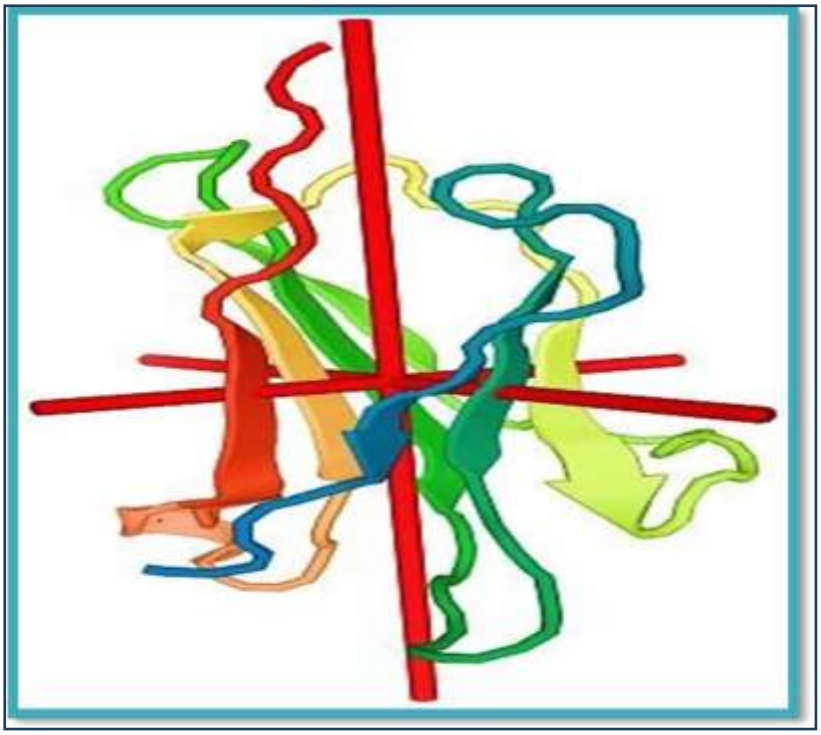

Figure (3): Molecular structure of β2-microglobulin (β2M).

Conclusion and recommendations:

We came to the conclusion that, in order to prevent potentially harmful sequences, the primary objective of the physician treating patients with ICH should be the early and accurate diagnosis of AKI. When patients in the intensive care unit (ICU) have intracerebral haemorrhage (ICH), B2-MG can be used as a predictive marker of the onset of AKI. highlighting the most recent guidelines for the diagnosis and treatment of these patients while taking into account the evaluation of β2-MG as a tool to achieve early detection of AKI in individuals with ICH. More research is required to fully examine this problem.

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