N-Acetyl-Beta-D-Glucosaminidase in Kidney Injury

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Contributor: Ruder Novak, Grgur Salai, Stela Hrkac, Ivana Kovacevic Vojtusek, Lovorka Grgurevic

Acute and chronic kidney diseases are an evolving continuum for which reliable biomarkers of early disease are lacking. The potential use of glycosidases, enzymes involved in carbohydrate metabolism, in kidney disease detection has been under investigation since the 1960s. N-acetyl-beta-D-glucosaminidase (NAG) is a glycosidase commonly found in proximal tubule epithelial cells (PTECs).

Keywords: N-acetyl-beta-D-glucosaminidase ; NAG ; chronic kidney disease

1. Introduction

The kidney is a vital organ with critical functions in maintaining body fluid balance, waste product secretion, hormone production, and acid-base and electrolyte homeostasis [1]. It makes up less than 1% of the total body mass and receives roughly a quarter of the cardiac blood output, making it susceptible to many toxic agents [2]. The workhorse of the kidney is the proximal tubule epithelial cell (PTEC) system, which performs much of the filtration and reabsorption, hence its role as a major starting point in both acute and chronic disease scenarios [3][4][5][6][7]. As renal tissue is stressed, multiple underlying mechanisms and molecular pathways can induce acute kidney damage that can, over time, lead to chronic kidney disease (CKD)—a worsening glomerular, tubular and/or vascular impairment [8]. Briefly, noxious stimuli cause injury to PTECs, which stimulate inflammation, recruit myofibroblasts, and produce a plethora of profibrogenic molecules that drive interstitial inflammation and fibrosis. Furthermore, uninjured tubular cells face an increased tubular transport workload, which leads to hypoxia, anaerobic metabolism utilization, and acidosis [6][9]. Renal tissue has limited regeneration capabilities, so the ensuing vicious cycle of damage-induced inflammation sustains fibrosis, which over time deteriorates tissue function, leading to end-stage renal disease and the need for kidney transplantation or dialysis [10].

Diagnosis of kidney disease currently relies on the estimation of functional parameters, such as glomerular filtration rate (GFR), kidney biopsies, or the more sensitive indicators such as detection of proteinuria or assessment of urinary enzymes [11]. The diverse etiology of CKD impedes our ability to predict the dynamics of its progression, its long-term outcomes, and adequate therapeutic approaches. As this global public health problem is not yet fully understood on the molecular level, many potential disease biomarkers have so far been extensively reviewed as possible early predictors of disease progression. The problem with using plasma biomarkers is that they usually reflect systemic endothelial dysfunction or inflammation; i.e., they are not specific biomarkers of kidney damage [12]. On the contrary, urinary biomarkers of tubular dysfunction show more promise in that regard. Recent efforts have focused on recognizing early tubular damage, that is, prior to PTEC injury and the appearance of any clinical and functional signs [13][14]. In that regard, the prediction of acute kidney injury (AKI) in patients at risk by the combined detection of urinary “acute kidney stress” molecules tissue inhibitor of metalloprotease-2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP7) was recently approved by the U.S. Food and Drug Administration [15][16]. The onset of tissue damage causes urinary secretion of further mediators that are traditionally divided into three groups: (a) PTEC enzymes (N-acetyl-beta-D-glucosaminidase (NAG), α-glutathione S-transferase, and γ-glutamyl transpeptidase-GGT), whose concentrations in urine rise as a result of stress-induced metabolic changes; (b) molecules that are specifically upregulated upon PTEC damage; and (c) urinary low-molecular-weight proteins, such as alpha-1 and beta-2 microglobulin, that are secreted elsewhere in the body, filtrated by the glomeruli, reabsorbed completely by the PTECs, and found in urine only in states of tubular dysfunction [17][18]. A promising early biomarker of tubular damage is the neutrophil gelatinase-associated lipocalin (NGAL) that can potentially differentiate between reversible and irreversible injury, with important implications in customizing the therapeutic approach [19]. Other molecules studied in this regard include the kidney injury molecule-1 (KIM-1), the liver-type fatty acid-binding protein (L-FABP), and interleukin-18 (IL-18); however, evidence from multiple clinical studies shows a variable potential to predict the initiation and/or progression of kidney injury [20][21].

2. NAG in Kidney Injury

2.1. NAG in the Setting of AKI

AKI is a common clinical entity whose main outcome is a rapid decline of renal function [22]. The clinical definition and classification of AKI are provided by the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines, which rely on changes in serum creatinine and urine output. The definition and treatment recommendations remain points of interest since there are limitations of a classification system based on creatinine in catabolic or sarcopenic patients [23][24]. AKI presents a clinical problem commonly faced by a majority of physicians, but it also presents a global healthcare problem, as it has been significantly associated with mortality, length of hospital stay, and healthcare cost. Furthermore, CKD is recognized as a common sequela of AKI. Even in resolved AKI, KDIGO guidelines suggest these patients should be considered as at increased risk of CKD [23].

AKI can originate from multiple causes such as decreased renal perfusion, renal tubule injury from toxins or obstruction, tubulointerstitial inflammation, and primary reduction in the glomerulus' filtering capacity. The majority of AKI cases are due to ischemia and toxins, which cause loss of integrity and polarity in the kidney epithelium, leading to necrosis and apoptosis. This, in turn, leads to inadequate filtration and filtrate leak, i.e., proteinuria and the possibility of subsequent identification of specific proteins in urine [25]. Even though early recognition of AKI is essential as it could improve patient outcomes, its early diagnosis remains a challenge [26][27]. Kidney injury starts by inducing biological and molecular changes that, over time, evolve into cellular damage [22]. Therefore, the discovery and validation of a reliable biomarker for AKI prediction and early diagnosis seems prudent, as it would allow early diagnosis and inform on the progression of AKI, thereby improving treatment strategies [28].

Among candidate molecules, NAG, more precisely its urine concentration, has been studied extensively [25]. Importantly, its elevated urine levels in kidney injury are an early sign of disease since they precede the elevation of serum creatinine, a sign of worsening renal filtration [29]. NAG has previously been described as one of the promising novel markers of AKI; however, further research was warranted in order for it to be validated, namely its efficacy in different age groups and its utility in the setting of different pathophysiological circumstances (e.g., drug-induced AKI, critically ill patients, etc.) [22]. In recent years, numerous studies addressing these questions have been published and show promising results.

Multiple recent studies have evaluated NAG as a marker of AKI in patients with cardiovascular diseases. In a study group of patients with chest pain, NAG was compared with other markers, such as creatinine and cystatin C, and was shown to be the only marker with a promising potential for AKI prediction. Its additional clinical value was also shown in its possibility to predict the necessity of renal replacement therapy [30]. In addition to acute cardiovascular settings, NAG has also been shown to indicate tubular injury in chronic heart failure [31]. Furthermore, Fujigaki et al. analyzed patients with AKI due to minimal change nephrotic syndrome (MCNS) by using immunohistochemical expression of vimentin as a marker of tubular injury and dedifferentiation. They found proximal convoluted tubules to be injured (vimentin-positive) and that the percentage of the positive tubules was positively correlated with urinary NAG (uNAG) in all patients, even the non-AKI group of MCNS patients. This suggests that uNAG levels may reflect the degree of subclinical tubular injury in some patient groups [32]. In addition to the diagnosis and prediction of AKI, identification of its etiology is also of importance in different clinical settings, as this provides the possibility of more accurate diagnosis and targeted treatment. This was demonstrated by Kim et al., who aimed to differentiate types of AKI in patients with decompensated liver cirrhosis, namely azotemia, hepatorenal syndrome, and acute tubular necrosis, using uNAG levels, which they found to be a marker specific to renal tubular damage in decompensated cirrhosis, thereby determining the underlying clinical entity and influencing the choice of treatment [33]. Efforts have also been made to evaluate whether combining uNAG, a marker of tubular injury, with existing markers of functional kidney damage improves models of AKI prediction in different patient groups. Ma et al. found that uNAG may be used in combination with serum cystatin C (sCysC), which reflects functional kidney damage, to predict AKI in septic patients [26]. The same combination has also been found to improve the predictive accuracy of AKI in post-operative neurosurgical patients. Similar results were obtained in a different multicentre study of critically ill patients [27]. Additionally, uNAG in combination with sCysC succeeded in improving the accuracy of AKI detection models and intensive care unit mortality prediction [34].

Its applicability as a marker of AKI has been studied in various age groups, which is illustrated by several studies, including the study of Bíró et al., which showed serial uNAG tests (at least 5 samples/patient) in a group of pediatric patients with neoplastic disorders to identify 1.5× more clinical and subclinical AKI episodes, with a relatively high sensitivity and specificity. They also highlighted that serial uNAG measurements decrease the number of false positives, which they mostly attributed to overhydration [35]. Increased levels of uNAG were also found in a study group of pediatric

patients with AKI. In the latter study, in addition to a diagnosis of AKI, uNAG was also an indicator of dialysis requirement [36].

In order to establish uNAG's predictive value for AKI in clinical use, the dependence of its levels on other parameters has to be evaluated, as well as its performance in acutely or critically ill patients. Changes in levels of thyroid hormones and blood glucose have been shown to influence uNAG levels [37][38]. However, targeted studies showed that this did not affect uNAG's ability to detect AKI. Namely, the results of Wang et al. and Liang et al. showed that blood glucose and HbA1c levels, as well as thyroid hormone levels, did not significantly affect the performance of uNAG for AKI detection [39][40].

The existing body of research shows promise for uNAG's role as an easily accessible marker for early detection, and even prediction, of AKI. These are crucial for treatment initiation, thereby facilitating better outcomes and, in some cases, prevention of CKD. However, the use of uNAG in AKI also has some limitations. Among others, as in all urinary sampling, obtaining adequate samples from oliguric or anuric patients presents a substantial challenge; conversely, hydration levels also seem to cause variations in uNAG levels, thus blurring the line of clinical significance. Additionally, a possible limitation of NAG is the fact that urinary excretion of the enzyme is elevated not only in acute but also in chronic glomerular diseases [22].

2.2. NAG in the Setting of CKD

CKD is a heterogeneous disease that may occur due to multiple underlying disorders and is defined by the KDIGO initiative as "abnormalities of kidney structure and/or function, present for over three months, with implications for health" [41][42][43]. Causes of the disease can vary from genetic heritability to diabetes, hypertension, and glomerulonephritis as well as heart disease, obesity, and old age [44][45]. CKD is a major health problem, affecting over 10% of the world's population, and is commonly stratified based on the glomerular filtration rate (GFR) and albuminuria [41][46][47]. GFR is considered to be the most important marker of kidney function; however, it is usually not directly measured but rather estimated (eGFR) based on equations employing the serum concentration of creatinine [48]. Combining eGFR with microalbuminuria increases the ability to predict progression toward end-stage renal disease (ESRD) [49][50]. However, due to the heterogeneity of CKD, new and precise biomarkers are needed in order to detect patients in whom interventions are needed in order to halt CKD progression. Furthermore, the clinical need for biomarkers of CKD progression is especially emphasized in patients with early disease; specifically, in whom eGFR exceeds 60 mL/min/m^2 [51][52]. Therefore, potential biomarkers of CKD are constantly being researched, often using various "omics" approaches, of which proteomics is the most prominent [53][54][55].

uNAG is a potential biomarker of early CKD. Several cross-sectional studies observed higher levels of uNAG in patients with CKD in comparison to healthy controls. Furthermore, in a nested case-control study performed by Kern et al., urinary NAG concentrations measured at the study baseline were successful predictors of micro- and macroalbuminuria in patients with type I diabetes mellitus. Additionally, Vaidya et al. found that lower uNAG levels were associated with regression of microalbuminuria in patients with type I diabetes mellitus [56][57]. Even though no association was found for uNAG, Lobato et al. found that NGAL and KIM-1 do seem to be good predictors of CKD progression [58]. In a prospective study conducted by Fufaa et al. on Pima Indians with type II diabetes mellitus, NGAL was significantly associated with ESRD and mortality, which was not observed for NAG [59]. Interestingly, in a study conducted by Hsu et al., neither of the tested tubular damage markers (NGAL, KIM-1, or NAG) did not improve the C-statistic of the baseline clinical prediction model for CKD progression, which employed eGFR and urine albumin to creatinine ratio [51][52]. Based on the available studies, it is clear that uNAG is not an optimal biomarker for CKD progression.

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