Novel kidney injury biomarkers in tropical infections: a review of the literature

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ABSTRACT

Tropical diseases are mainly found in the tropical regions of Asia, Africa and Latin America. They are a major Public Health problem in these regions, most of them are considered neglected diseases and remain as important contributors to the development of AKI (Acute Kidney Injury), which is associated with increased patients’ morbidity and mortality. In most countries, kidney disease associated to tropical diseases is attended at health services with poor infrastructure and inadequate preventive measures. The long-term impacts of these infections on kidney tissue may be a main cause of future kidney disease in these patients. Therefore, the investigation of novel kidney injury biomarkers in these tropical diseases is of utmost importance to explain the mechanisms of kidney injury, to improve their diagnosis and prognosis, as well as the assessment to health systems by these patients. Since 2011, our group has been studying renal biomarkers in visceral and cutaneous leishmaniasis, schistosomiasis, leptospirosis and leprosy. This study has increased the knowledge on the pathophysiology of kidney disease in the presence of these infections and has contributed to the early diagnosis of kidney injury, pointing to glomerular, endothelial and inflammatory involvement as the main causes of the mechanisms leading to nephropathy and clinical complications. Future perspectives comprise establishing long-term cohort groups to assess the development of kidney disease and the patients’ survival, as well as the use of new biomarkers such as urinary exosomes to detect risk groups and to understand the progression of kidney injuries.

KEYWORDS: Acute kidney injury. Biomarkers. Chronic kidney disease. Diagnosis. Hemodialysis. Neglected diseases. Neglected tropical diseases.

INTRODUCTION

Tropical infections are important causes of morbidity and mortality and a major public health problem, especially in tropical regions of Asia, Africa and Latin America. Kidneys may be injured on several occasions, complicating the course of many infectious and parasitic diseases¹. Several types of renal abnormalities have been observed in patients with tropical diseases, including visceral leishmaniasis (kala-azar), dengue, leprosy, schistosomiasis, malaria and leptospirosis².

Although several types of nephropathies are detected in tropical diseases in different clinical contexts, the diagnosis of renal dysfunction is almost always late, being an important cause of medical complications. Moreover, the long-term impact of these infections on kidney tissues have never been investigated and may be a major cause of future kidney disease.
Kidney injury mechanisms are not fully understood in many cases bringing major difficulties to specific therapeutic interventions. Worldwide, kidney injury identification is difficult, partly because of the low sensitivity of traditional diagnostic tests, such as serum creatinine measurement, being the condition often diagnosed only when the disease is fully established, with clear clinical signs and symptoms of renal dysfunction.

Thus, it is of utmost importance to investigate new biomarkers that may be associated with the early identification of nephropathies observed in these infectious diseases. Many of these new renal biomarkers have been widely studied in the most common renal diseases but have been scarcely investigated in tropical diseases. Among them, the serum and urinary Neutrophil Gelatinase-Associated Lipocalin (NGAL), urinary Monocyte chemotactic peptide-1 (MCP-1), urinary Vascular Endothelial Growth Factor (VEGF) and serum Fibroblast Growth Factor-23 (FGF-23) are potential new renal biomarkers. These renal biomarkers can provide important information regarding the location and chronicity of the kidney injury, and the early and specific identification of injury mechanism.

Moreover, due to the particular characteristics of tropical diseases, other variables have become of great importance, such as inflammatory mediators and endothelial biomarkers, which are involved in several glomerulopathies. Proteinuria, for instance, may be the result of the loss of the glomerular endothelial glycocalyx layer, which is rich in negatively charged proteoglycans. The release of syndecan-1 in plasma is a biomarker of endothelial glycocalyx injury that is present in these alterations. Inflammatory mediators, such as interferon-gamma (IFN-γ), C-reactive protein (CRP), and interleukins 6 and 17 (IL-6; IL-17) are associated with renal events in infectious diseases such as visceral leishmaniasis, dengue hemorrhagic fever and leprosy.

**METHODS**

This is a review of the literature on articles regarding kidney involvement in tropical diseases with focus on novel biomarkers of kidney injury, which are crucial for detecting this complication as early as possible. We have used the terms “acute kidney injury”, “kidney diseases”, “biomarkers”, “neglected diseases” and the following infections: leishmaniasis, leprosy, schistosomiasis, leptospirosis and dengue. PubMed was the database we have used to perform the search, and the study comprised the period 2010-2019. We have also included the studies from our group to summarize the biomarkers we have investigated throughout the past years in the field of tropical infections.

**RESULTS**

**Tropical diseases and kidney complications**

Tropical infections continue to be an important cause of renal dysfunction, and some diseases show a significant frequency of acute kidney injury (AKI). It is likely that kidneys are particularly vulnerable to heat stress and to the re-emergence of water- and vector-borne infectious diseases. Examples include leptospirosis, leishmaniasis, leprosy, dengue, malaria and schistosomiasis. The contribution of AKI associated with infection in relation to other CKD factors has never been systematically evaluated. Research is needed to quantify the impact of infections on kidney health through prospective and cohort studies.

**Dengue**

Dengue is the most important mosquito-borne viral disease that affects humans in the tropical and subtropical regions worldwide. The infection can be asymptomatic or severe and fatal manifesting as dengue hemorrhagic fever (DHF), which is characterized by hemorrhagic events, thrombocytopenia and shock. During DHF, viral antigens have already been detected in several organs, including the kidneys. Most studies of renal involvement during dengue infection have reported considerable mortality rates, especially in DHF. Glomerular biopsies show abnormalities such as hypertrophy and hyperplasia of mesangial and endothelial cells in some glomerular capillary lumens and focal thickening of the glomerular basement membrane. In other cases, immune complex deposition in the glomerulus is a common histological finding. Vascular alterations have also been observed and seem to be related to the imbalance of the host’s immune response, as a consequence of the cytokines release profile and the type of cells present at the lesion sites.

There are few studies on novel kidney injury biomarkers in dengue. Neutrophil gelatinase-associated lipocalin (NGAL) and resistin, a molecule associated to inflammation, were significantly more elevated in patients with dengue, in comparison with healthy subjects.

**Leishmaniasis**

Visceral leishmaniasis (kala-azar) is a chronic and lethal parasitic disease caused by intracellular parasites of the genus *Leishmania*. This is a zoonotic disease, typical of tropical areas, caused by *Leishmania leishmania infantum chagasi*, which is transmitted through a vector, an insect of the genus *Lutzomyia*.
Leishmania causes intense parasitism of the reticuloendothelial system and can be found in the liver, spleen, bone marrow, lymph nodes, lungs, kidneys and intestine. As a consequence of the parasitism, the patient has accentuated anemia, leukopenia, thrombocytopenia and increased plasma gamma globulin levels.

Renal involvement in chronic visceral leishmaniasis (VL) is often associated with the progression of infection and increased mortality in these patients. The development of AKI hinders the clinical management of patients with VL and is associated to increased length of hospital stay, poor prognosis and mortality.

In one of the first studies on VL nephropathy, the presence of proteinuria < 1g/24h (57%), hematuria or leukocyturia (51%) were reported in 50 patients. When performing the analysis of clinical findings due to renal dysfunction associated to VL in the literature, the following was observed: moderate proteinuria, hematuria, leukocyturia, microscopic hematuria, hydroelectrolytic disorders such as hyponatremia, hypokalemia, hypochloremia, hypocalcemia, hypomagnesemia, increased excretion fraction of several electrolytes, and defects in urinary concentration and acidification. There is an induction of B-cell humoral immune activity, which has been associated with glomerular disease in kala-azar. Consequently, antibodies produced in response to the infection may lead to immune complexes formation that deposit in the glomerulus and may induce a local inflammatory response, causing renal functional and structural abnormalities.

Cutaneous leishmaniasis (CL) shows fewer renal alterations, as evidenced in the literature. The kidney injury mechanism that may occur also seems to be mediated by the deposition of immune complexes, formed after parasite destruction and formation of Donovan bodies. AKI occurs at a much lower frequency in CL when compared to VL, and seems to be more associated to the leishmanicidal treatment.

An important study of our group in 37 patients with CL observed changes in the glomerular filtration rate and, especially, tubular defects, including defects in urinary concentration and acidification, as well as changes in the fraction of sodium, potassium, calcium and phosphorus excretions.

Leprosy

Leprosy is another infectious disease with chronic evolution that has affected humanity for millennia, and to this day remains a major public health problem in many countries worldwide. The disease is caused by Mycobacterium leprae, an acid-fast bacillus, a mandatory intracellular microorganism that mainly affects the skin and peripheral nervous system, causing a wide variety of clinical and histopathological manifestations. Depending on the degree and efficacy of cell-mediated immunity, patients may present with a single, well-delineated lesion (tuberculoid pole - paucibacillary) or, at the other end, with many and poorly delineated lesions of several types, such as papules, nodules, and macules (virchowian pole -multibacillary).

The disease is currently divided into four clinical forms, according to the World Health Organization (WHO) criteria: undetermined, tuberculoid, dimorphic and Virchowian.

Renal lesions in patients with leprosy were initially studied in autopsies of infected patients. The rate of renal alterations can be as high as 72% in these patients, especially in the Virchowian form, which is the most severe form of the disease. Although clinical renal complications are uncommon and usually mild when present, they may be silent, as they have never been investigated, constituting long-term risk factors for the development of Chronic Kidney Disease in these patients.

Only a few patients show a rapid decline in renal function or large proteinuria associated with edema. These uncommon cases were presented as case reports due to their rarity. Glomerulonephritis seems to be the most common type of nephropathy in leprosy, accompanied by hematuria and increased proteinuria, especially in multibacillary forms.

The exact mechanism leading to the development of glomerulopathy is not completely understood. M. leprae does not seem to be directly involved, although it has already been found in the glomeruli of some patients. The most common glomerular histological change is mesangial proliferative glomerulonephritis, which is often associated to immune complex depositions.

Leptospirosis

Leptospirosis is a disease caused by a microorganism of the genus Leptospira. In total, nine pathogenic species are known, including L. interrogans. The early phase of leptospirosis manifestations lasts three to seven days and includes fever, headaches, myalgia (especially in calves), nausea, vomiting, malaise and conjunctival hyperemia. Only 10% might progress to the second phase: Weil’s syndrome, which lasts from four to 30 days, showing more severe symptoms, such as jaundice, meningitis, pulmonary hemorrhage and acute kidney injury.

The kidney is one of the main targets of Leptospira, and kidney injury can occur in 20-85% of patients. Clinical manifestations range from simple urinary sediment abnormalities to acute renal failure. Renal and glomerular tubular involvement may occur through several mechanisms, such as direct nephrotoxic action.
of *Leptospira*, hemodynamic alterations and decreased glomerular filtration rate and rhabdomyolysis\(^9\). Loss of urinary electrolytes may lead to hypomagnesemia and hypokalemia and tubular alterations usually precede the decrease in the GFR. AKI in leptospirosis is often non-oliguric and hypokalemic. The etiopathology of AKI is complex and multifactorial, including the direct effect of the bacterium on renal tissues, hypovolemia, hypotension, rhabdomyolysis, hyperbilirubinemia and endothelial glycocalyx damage\(^1,2\). Novel biomarkers in leptospirosis have been investigated, including neutrophil gelatinase-associated lipocalin (NGAL), significantly associated to endothelial damage biomarkers (syndecan-1 and ICAM-1)\(^9\).

Malaria

Malaria is an important tropical disease, with great concern for Public Health, with most cases concentrated in Africa and in the Amazon forest region\(^37-39\). Malaria is associated to disease in glomeruli, tubules and in the interstitial region\(^39\). AKI in malaria is more frequent in infections caused by *Plasmodium falciparum*, and manifestations include oliguria, severe metabolic acidosis, hypercatabolic state and hydroelectrolytic disorders, such as hyponatremia and hyperkalemia\(^39\). The histopathological findings in malaria-associated AKI include acute tubular necrosis, interstitial nephritis, inflammatory interstitial infiltrate, edema and glomerulonephritis, and the pathogenesis is associated to blockade of renal microcirculation, hemodynamic factors and hypovolemia\(^40-42\).

Malaria was one of the first parasitic diseases described to be a directly involved with glomerulonephritis\(^39\), and proteinuria is a frequent finding among infected patients, varying from 20 to 50% of cases\(^43\). Mesangial proliferation is the most frequent found pattern, with mild matrix expansion and deposits of eosinophilic material on the capillary walls in the mesangium and in Bowman’s capsule. Immunofluorescence shows granular deposits of IgM and C2 in the capillaries and mesangium\(^43,44\). Collapsing focal and segmental glomerulosclerosis is a less frequent lesion observed in malaria, with a non-immune pattern\(^45\).

There are few studies investigating novel kidney injury biomarkers in malaria. Neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1) have been investigated in *P. falciparum* infections\(^46\). Another study found increased KIM-1 and matrix metalloproteinase-3 (MMP-3) expression in tissues from autopsied patients with malaria-associated AKI\(^47\). Chitinase-3-like 1 (CHI3L1), a glycoprotein that has been recently proposed as a urinary biomarker for AKI, was also associated to AKI in children with severe malaria, and evidenced its association with mortality\(^48\). Approximately 31% of patients with malaria-associated AKI had normal levels of creatinine at presentation, illustrating the importance of new AKI biomarkers\(^49\).

Schistosomiasis

*Schistosoma mansoni* infection remains a major public health problem, affecting approximately 200 million people in more than 70 countries, mainly in Africa, Eastern Mediterranean and South America\(^49\).

Renal involvement in schistosomiasis is mainly described by a glomerular involvement. Schistosomal glomerulopathy is associated to the hepatosplenic form of the disease, but it has also been observed in the hepatic intestinal form\(^50\). The immunological nature of the glomerular involvement in schistosomiasis is well established. The most frequently reported histological types are chronic membranoproliferative glomerulonephritis, segmental and focal glomerulosclerosis, usually associated to nephrotic syndromes\(^51\). Besides the parasites antigens, there are other important factors that seem to contribute to the pathogenesis of glomerular diseases in schistosomiasis, such as the collateral circulation of the portal system due to the degree of hepatic involvement, the inefficiency of the hepatic macrophage system, the severity and duration of the infestation and genetic factors\(^52\). Monocyte Chemotactic Protein-1 (MCP-1) has been investigated in chronic schistosomiasis caused by *S. mansoni*, and there is evidence of association to subclinical kidney disease, with significant association to albuminuria\(^53\).

The importance of early renal injury diagnosis

Until recently, there were over thirty definitions of AKI in the literature, rendering comparisons of results among studies very difficult. The absence of a universally accepted definition resulted in a huge variation in the described incidence of AKI, rendering comparisons between different studies and populations difficult\(^8\). In 2004, the ADQI (Acute Dialysis Quality Initiative) group proposed a consensual definition for AKI: the RIFLE (Risk, Injury, Failure, Loss and End-stage Kidney Disease) classification. This is a classification system based on acute changes in serum creatinine measurements and/or variations in diuresis. It has three classes of severity (Risk, Injury and Failure) and two classes of evolution (loss and end-stage kidney disease)\(^54\). In 2007, the Acute Kidney Injury Network (AKIN) classification was proposed, and revised this definition, suggesting minor changes based on the abrupt decrease in renal function (within 48 h) and establishing a
staging system in an attempt to define the degrees of renal dysfunction at the moment of diagnosis\textsuperscript{54,55}.

More recently, the Kidney Disease Improving Global Outcomes (KDIGO) group has proposed a new definition including the increase in serum creatinine (0.3 mg/dL) during a 48-h period, similar to the definition proposed by the AKIN group. In addition, a 50% increase in serum creatinine is considered within a seven days period, as suggested by the RIFLE criterion\textsuperscript{56}.

However, the diagnosis of renal disease based on serum creatinine is still a late diagnosis, contributing to the high rates of AKI\textsuperscript{57}. Clinical markers used to assess renal function, such as urinary volume and serum creatinine, are very limited due to extrarenal variables that interfere with their levels, and creatinine increases only occurs when half of the renal function is already impaired\textsuperscript{58}.

Thus, the identification of kidney injury also becomes difficult due to the low sensitivity of diagnostic tests, being often diagnosed only when it is fully established, with evident clinical signs and symptoms. Early detection of patients at increased risk for acute renal dysfunction may be decisive for changing the clinical management and increasing patients’ survival, thus reducing the incidence of unfavorable outcomes\textsuperscript{58}. As a result, there has been an exponential increase in studies with new AKI biomarkers that could be earlier and more specific markers of kidney injury\textsuperscript{59}.

Novel kidney injury biomarkers

Studies on new kidney injury biomarkers aimed to obtain important information regarding the location of the kidney injury, assessing the injury intensity, the differential diagnosis of the injury, its predictive capacity of AKI in new or hospitalized patients and the impacts of therapeutic interventions. Several new biomarkers candidates are being studied in different clinical contexts, showing greater specificity and sensitivity in relation to classic clinical renal markers\textsuperscript{60}. They can be quantified in serum and urine samples, showing relevant results in both cases. Urine is ideal for these diagnostic and prognostic studies, as it is a noninvasive and easily collected biological specimen whereas serum is also an important specimen, as its systemic biomarkers can influence urinary levels or even be associated with kidney disease\textsuperscript{61,62}.

Each new biomarker has advantages and disadvantages, but they are usually more specific to a specific part of the nephron, helping to detect the site of kidney injury and elucidate the nephrotoxic mechanisms. The combined evaluation of several biomarkers in the same clinical context can complement the pathophysiological information of each one of the parameters and improve not only the understanding of the nephropathy but also its clinical diagnosis\textsuperscript{63}.

For AKI, the most often studied biomarkers are Neutrophil Gelatinase-Associated Lipocalin (NGAL), Kidney Injury Molecule-1 (KIM-1), FABP1 (Fatty Acid-Binding Protein 1) and FGF-23 (fibroblast growth factor 23) (LEAF 2016). Other biomarkers are more specific for glomerulopathies\textsuperscript{63-66}.

Use of new biomarkers in tropical diseases

Despite the increased risk of kidney disease and the infectious characteristic of tropical diseases, the use of new biomarkers for the detection and evaluation of prognosis in these patients has been scarce and has not followed the same pace as in other clinical contexts. In fact, this also characterizes these tropical diseases as neglected diseases for health services. Our group has been studying renal pathophysiology in these diseases and has evaluated different types of biomarkers over the past eight years, which could broaden the knowledge on the type of kidney injury, its early detection, risk groups for kidney disease and the mechanisms of kidney injury. Patients with cutaneous and visceral leishmaniasis, leptospirosis, schistosomiasis, and leprosy have already been studied.

In 2011, renal tubular dysfunction was shown for the first time in patients with Cutaneous Leishmaniasis (CL), as well as the association with the altered expression of renal tubular transporters and compensatory mechanisms of these dysfunctions\textsuperscript{67}. In this study, urinary exosomes were evaluated to elucidate the etiology of urinary concentration and acidification failure found in apparently asymptomatic patients\textsuperscript{67}. It was observed that defects in urinary concentration were caused by a decrease in the expression of aquaporins (AQP2), accompanied by a compensatory increase of the NKCC2 transporter, responsible for sodium, potassium and chloride absorption into the interstitium, indicating problems of the AQP2 production in the collecting duct (Figure 1). On the other hand, acidification defects were evidenced by the increase in the apical exchanger pendrin of β-intercalated cells in the cortical collecting duct. The pendrin secretes bicarbonate in the lumen and increases the urinary pH. Moreover, compensatory mechanisms have also been demonstrated due to the increase in the NHE3 exchanger, which secretes H⁺ ions in the lumen (Figure 1). However, the stratification of patients with these alterations and their long-term impacts on renal function has not yet been studied.

Glomerular involvement is very present in infectious diseases such as VL, and can be decisive for the development
of AKI, contributing to the poor patient’s prognosis. The investigation and elucidation of the mechanisms involved in glomerular structural and functional alterations may also help in the discovery of new kidney injury biomarkers and new therapeutic targets for these glomerulopathies.

In 2014, in a prospective study, we showed high levels of urinary MCP-1 and urinary oxidative stress in patients with visceral leishmaniasis who had normal serum creatinine, suggesting the presence of glomerular inflammation and incipient renal damage. Another biomarker that seems to be reliable for the early detection of subclinical kidney injury in tropical diseases is NGAL, which had a good accuracy in a recent study from our group.

Another study from our group showed early glomerular inflammation associated to increased proteinuria, albuminuria and renal oxidative stress in patients with leprosy, especially those with the virchowian form, suggesting that these patients had an increased risk of developing clinical kidney disease.

A summary of the main tropical infections, the novel biomarkers that have been already investigated and their implications in clinical practice is shown in Table 1.

CONCLUSION

Tropical infections are currently one of the most worrying problems in Public Health, greatly impacting on the development of kidney diseases and their complications. Biomarkers aiming to the early detection of kidney injury are crucial to help decreasing the burden of kidney diseases, especially in the developing world, where tropical diseases are most common and access to healthcare is often difficult, including access to kidney diseases treatment. Hence, early detection of kidney disease is crucial.

Figure 1 - At the top: Plenty of (a) aquaporin (AQP2); (b) Na-K-2Cl cotransporter (NKCC2); (c) pendrin; (d) Na / H exchanger (NHE3). Adapted from Oliveira et al. with permission, ©2011 International Society of Nephrology / Elsevier. At the bottom of (b), (c) and (d): Western blotting analysis of the urinary exosome fraction, normalized according to the urinary creatinine, in controls and in patients with American cutaneous leishmaniasis.
injury can prevent kidney disease progression, avoiding the need of expensive treatments such as dialysis and transplantation. It is possible that in the future, a “panel” of kidney injury biomarkers will be used in clinical practice, enabling the detection of any subclinical injury, from the glomeruli to any portion of the renal tubules.

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| Table 1 - Tropical infections and novel biomarkers of acute kidney injury. |
| Infection     | Kidney involvement | Novel biomarkers already investigated | Usefulness of the novel biomarkers |
|---------------|--------------------|--------------------------------------|----------------------------------|
| Dengue        | AKI                | NGAL, resistin                       | Higher among patients with dengue, evidence of inflammation. |
| Leishmaniasis | AKI, proteinuria, hematuria, leukocyturia, hydroelectrolytic disorders, defects in urinary concentration and acidification. | AQP2, NKCC2, NHE3 | Detection of defects in tubular transport. |
| Leprosy       | Proteinuria, Glomerulonephritis, AKI/CKD. | MCP-1 | Association to AKI, multibacillary forms and oxidative stress. |
| Leptospirosis | AKI                | NGAL, Syndecan-1, ICAM-1             | AKI, Endothelial damage. |
| Malaria       | AKI, Glomerulonephritis (mesangial proliferation, segmental and focal glomerulosclerosis) | NGAL, KIM-1, MMP-3, CHI3L1 | Early detection of malaria-associated AKI; Association to mortality. |
| Schistosomiasis | Glomerulonephritis (membranoproliferative glomerulonephritis, segmental and focal glomerulosclerosis) | MCP-1 | Association to subclinical kidney disease, inflammation and albuminuria. |

AQP2 = aquaporin 2; CHI3L1 = matrix metalloproteinase-3; NGAL = Neutrophil gelatinase-associated lipocalin; NKCC2 = Na-K-Cl co-transporter; KIM-1 = kidney injury molecule-1; MCP-1 = monocyte chemotactic protein-1; NHE3 = Na/H co-transporter.
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