Urinary transferrin as a marker of renal injury in diabetic individuals: an integrative review

ABSTRACT

Chronic Kidney Disease (CKD) poses a significant challenge to public health, with diabetes mellitus emerging as the second leading etiological factor, as evidenced by the latest Brazilian Dialysis Census. CKD exhibits a strong association with obesity, hypertension, and familial predisposition. While microalbuminuria traditionally serves as a diagnostic marker for diabetic nephropathy (DN), its diagnostic shortcomings, including delayed onset and lack of specificity for Diabetic Kidney Disease (DKD) and CKD progression, necessitate the exploration of alternative biomarkers. Over the past two decades, researchers have investigated urinary biomarkers, notably urinary transferrin, which shares similarities with albumin but demonstrates enhanced glomerular filtration. This integrative review aims to evaluate the clinical-laboratory utility of transferrin as a biomarker for kidney injury. The findings suggest that urinary transferrin may exhibit superior sensitivity in identifying glomerular damage in diabetic patients compared to microalbuminuria, serving as an early indicator of DN and predicting the onset of microalbuminuria and progression of CKD. However, its lack of specificity for DN warrants further investigation. This study underscores the necessity of elucidating the role of urinary transferrin as an experimental laboratory marker for kidney injury in diabetic patients, emphasizing the imperative to transition from discovery to validation of novel urinary biomarkers and to develop diagnostic methodologies that incorporate urinary transferrin as a biomarker for early DN diagnosis.

Keywords: Diabetes mellitus, biomarker, urinary albumin, urinary transferrin.

INTRODUCTION

Chronic Kidney Disease (CKD) is a public health issue. The Brazilian Society of Nephrology, through the 2022 Brazilian Dialysis Census, disclosed that approximately 153,831 Brazilians were undergoing chronic dialysis treatment in 2022, with Systemic Arterial Hypertension (SAH) being the primary cause (33%) and Diabetes Mellitus (DM) the second leading cause (32% of cases). Together, DM and SAH accounted for

two-thirds of the underlying diseases leading to chronic kidney failure (CKF) in Brazil. (1) Here it's worth highlighting that DM is one of the causes of SAH, meaning a significant portion of SAH cases stem from DM. Given this scenario, it's possible to suggest that renal complications secondary to DM could be the leading cause of CKD in Brazil.

It's estimated that 20% to 40% of diabetic patients will eventually develop renal complications known as Diabetic Kidney Disease (DKD). The progression from diabetes to DKD is influenced by genetic, behavioral, ethnic, and environmental factors (2).

The morphofunctional alterations in DKD, known as Diabetic Nephropathy (DN), are characterized by thickening of the glomerular and tubular basement membrane, leading to glomerulosclerosis and tubulointerstitial fibrosis with increased urinary protein excretion (3) Therefore, the genesis of proteinuria may be related to both glomerular and tubular alterations.

Low molecular weight proteins (LMWP) from glomerular filtration are reabsorbed by the proximal tubule through receptor-mediated endocytosis (4). Among LMWPs, albumin and transferrin stand out. Three receptors are involved in this process: megalin, cubilin, and amnionless, which together form a multiligand receptor complex (MRC) (5).

The endocytosis process begins with the binding of LMWPs to the MRC present on the apical membrane of proximal tubular cells. Subsequently, internalization occurs, forming the primary endosome with a pH of 6.5. Endosomal acidification is essential for the dissociation of LMWPs from the MRC. Upon dissociation, the MRC recycles back to the luminal membrane, becoming available for a new endocytosis process. The LMWPs follow the lysosomal pathway, where they are degraded into amino acids or, in smaller amounts, proceed through the transcytosis pathway. Endosomal acidification is achieved by the influx of H^+ facilitated by the V-type H^+-ATPase in parallel with the influx of Cl^- carried out by the ClC-5 and CFTR transporters. This Cl^- current neutralizes the potential difference generated by the H^+-ATPase, ensuring its proper function and endosomal acidification (Figure 1). (6).

Figueira and colleagues demonstrated that diabetic rats for 4 weeks showed reduced cortical expression of megalin, cubilin, ClC-5, and CFTR, associated with increased urinary excretion of albumin and transferrin. These data suggest a contribution of proximal tubular endocytosis dysfunction to proteinuria formation in

diabetic individuals, not solely attributable to the glomerulus, as previously suggested (7).

Despite the various pieces of evidence showing that DKD involves complex glomerular, tubular, and vascular morphofunctional changes, the diagnosis of CKD is still primarily based on glomerular function estimates, such as calculating the Glomerular Filtration Rate (GFR) using creatinine clearance, and urinary excretion os albumin. While an important tool, these methods has significant limitations as it doesn't allow for the determination of alterations in tubular reabsorption and secretion mechanisms (8, 9).

Urinary albumin excretion values below 30 mg/day are considered normal. Values between 30-300 mg/day are classified as microalbuminuria, and values above 300 mg/day as macroalbuminuria (10). There is a frequent misinterpretation by some professionals that increased urinary albumin excretion is a direct and exclusive consequence of functional changes in the glomeruli. Current literature demonstrates that in cases of micro or macroalbuminuria, functional and/or structural alterations occur in both glomeruli and proximal tubules. There is also evidence suggesting an increase in urinary albumin excretion related to functional alterations solely in the proximal tubule (11, 12).

Biopsy is considered the gold standard technique for diagnosing CKD and DN, used when laboratory and imaging tests fail to provide sufficiently clear information for diagnosis. However, due to the invasive nature of this approach, which poses risks of organ loss due to procedure-related complications, alongside higher costs related to hospitalization and the need for a skilled medical professional, renal biopsy is not frequently employed in clinical practice (13).

On the other hand, urinary albumin excretion is considered the non-invasive gold standard for detecting CKD and cardiovascular diseases. While not the most efficient marker for kidney injury, microalbuminuria stands out as a significant predictor for progression to end-stage renal disease in diabetic patients (14-16).

Some patients without microalbuminuria displayed advanced renal pathological changes, suggesting that microalbuminuria might not be an ideal marker for early detection of DKD (17, 18). Additionally, in some cases, diabetic patients may experience progressive loss of renal function before the development of microalbuminuria (19). These findings emphasize the complexity of DKD progression

in diabetic patients and the need to consider multiple indicators for comprehensive assessment.

Furthermore, microalbuminuria is not specific to the presence of DKD as it can occur in patients with DM without Diabetic Nephropathy (DN). Hence, the study of other more specific markers becomes necessary (20, 21).

Transferrin is a plasma protein with a molecular weight (MW) of 76.5 kDa and a molecular radius of 4 nm. However, concerning filtration across the glomerular barrier, transferrin is filtered more rapidly than albumin, which has a MW around 65 kDa and a molecular radius of 3.6 nm. This increased filtrability is related to the fact that transferrin has a lower anionic charge, favoring its filtration through the highly anionic glomerular basement membrane (22).

Urinary transferrin is considered an experimental biomarker more sensitive to glomerular and proximal tubular damage in diabetic patients. Urinary transferrin excretion shows a strong linear relationship with urinary albumin excretion in diabetic patients, and an increase in urinary transferrin predicts the development of microalbuminuria in type 2 diabetic patients with normoalbuminuria (22).

Studies indicate that in type 2 diabetes patients, urinary transferrin significantly increases with the progression of diffuse glomerular lesions, a phenomenon confirmed through renal biopsies. Additionally, it was observed that some patients with diffuse glomerular lesions, even in the absence of microalbuminuria, showed microtransferrinuria (23, 24). In another study, urinary transferrin excretion was also correlated with the degree of interstitial fibrosis, tubular atrophy, and infiltration of inflammatory cells in the interstitial space (23, 24). These findings suggest that evaluating urinary transferrin can provide valuable insights into the status of renal lesions in type 2 diabetic patients, even in early stages of the disease.

The main objective of this work is to present the relationship of urinary transferrin as a potential clinical-laboratory marker of renal injury in diabetic patients, using an integrative review.

METHODOLOGY

The research conducted was an integrative review, following the definition from the Cochrane Library. To guide this study, a checklist recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline was used for a critical and comprehensive assessment of the study (25, 26). The approach

followed the PICO model, where P represents Participants (patients), I Intervention, C Comparison, and O Outcome (27).

The main question that guided this review was the relationship of urinary transferrin as a clinical-laboratory marker of kidney injury in diabetic individuals.

Data were collected through searches in the databases Pubmed, Scopus, Cinahl, Web of Science, and The Cochrane Database, using English descriptors selected from the Medical Subject Headings (MeSH). The search strategy involved terms such as "Clinical research," "Biomarker," "Diabetes Mellitus," "Albumin," and "Transferrin," combined with the boolean operators "AND" or "e."

The Rayyan platform was used for study analysis by title, abstract, and subject, with all the mentioned keywords. Exclusion criteria and evaluation of scientific evidence were applied through the Critical Appraisal Skills Program (CASP), aiming to filter out studies not relevant to the research objective (28-30).

The inclusion criteria were: a) Randomized clinical trials related to the mentioned descriptors; b) Articles from national and international databases, in English and; c) Studies that evaluated urinary samples. The exclusion criteria were: I) Research with interventions different from those related to the descriptors; II) Studies that did not use urinary samples; III) Research with a different methodological design and; IV) Duplicate articles.

The inclusion period for studies was from January 2002 to December 2021, aiming to ensure relevance, methodological consistency, and alignment with the specific objectives of the integrative review.

After pre-selecting articles and excluding based on established criteria, an instrument for data collection was employed, including information such as name, title, objective, and methodology of each study. To ensure the reliability of the selected studies, the methodological structure of each article was evaluated using the Consolidated Standards of Reporting Trials (CONSORT). This reporting guideline is based on recent methodological evidence and provides a set of recommendations with 35 items, guiding the presentation of randomized clinical trials. Its purpose is to facilitate the applicability of conclusions obtained from the research question.

Additionally, a checklist for critical appraisal was adopted, covering areas of validity, results, and clinical relevance. This assessment was carried out through the Critical Appraisal Skills Program (CASP), which uses specific questions to critically analyze the methodological quality of studies included in the integrative review. This

procedure was employed with the aim of ensuring the robustness and reliability of conclusions drawn from the selected articles. After the preliminary selection from the database of published articles, the pre-selected studies were analyzed in full.

RESULTS AND DISCUSSION

The 17 analyzed studies were published between the years 2002 and 2011. During this period, the distribution of publications was as follows: from 2005 to 2011, 2016, and 2018, no articles related to the topic were published; in the years 2002 to 2004, 2012, 2014, and 2019, one article was published each year in each of those years; in the years 2013, 2015, 2017, and 2021, two articles were published per year; and in 2020, three articles were published on the subject. These data reveal a low quantity of publications in the literature addressing transferrin as a possible early urinary marker of renal injury in diabetic patients.

In Figure 2, represented by the geopolitical distribution of the publications, the studies are concentrated in countries of the northern hemisphere but also in the Americas. It is noteworthy that China is the country with the most research on the topic, totaling 4 articles, followed by the United Kingdom with 3 articles. It is pointed out that through the search strategy used by this study, no productions were found in Africa, Russia, Oceania, and Antarctica.

The identified articles were examined in full, covering various biomarkers, as outlined in Table 1. These biomarkers are categorized into markers of renal injury associated with glomerular, tubular, and podocyte damage, as well as indicative of damage from oxidative stress and inflammation, and others.

The results highlighted urinary markers that employed urinary albumin as an indicator for diagnosis and monitoring in diabetic individuals. The studies compared groups of normoalbuminuric, microalbuminuric, and macroalbuminuric individuals, using albumin as a urinary marker already established and standardized in the literature and clinical practice as a reference point. Despite conflicting scientific evidence, albumin is still recognized in clinical practice as an early marker of renal injury in diabetic individuals. The detection of urinary albumin in these individuals defines the diagnosis of diabetic nephropathy and is also used as a tool to monitor the progression of diabetic kidney disease (5, 22, 31).

In all chosen and analyzed articles, urinary transferrin was compared with urinary albumin. Urinary excretion of transferrin is higher in diabetic individuals, even

before the development of microalbuminuria, and the albumin/transferrin ratio is significantly lower in normoalbuminuric and microalbuminuric patients compared to macroalbuminuric patients. This indicates that urinary transferrin is considered a more sensitive marker of glomerular and proximal tubular damage. Furthermore, increased urinary excretion of transferrin anticipates the development of microalbuminuria in type 2 diabetic patients with normoalbuminuria (22).

Comparative evaluation of urinary transferrin with other biomarkers (RBP and serum osteopontin) revealed quite satisfactory diagnostic accuracy (32).

Increased urinary excretion of transferrin predicted the development of microalbuminuria in a cohort of normoalbuminuric type 2 diabetic patients, regardless of age, duration of diabetes, blood pressure, HbA1c, and baseline lipid levels (33).

Urinary transferrin is correlated with subclinical atherogenesis in type 2 DM patients without renal failury, suggesting its potential to identify cardiovascular risk in patients at an early stage of nephropathy without microalbuminuria (34).

Transferrinuria has been more extensively studied in type 2 diabetes patients, although it has been observed in a study involving type 1 diabetes patients (35).

Figure 3 summarizes the main findings related to urinary transferrin excretion compared to urinary albumin excretion in control individuals and normo, micro, and macroalbuminuric diabetic individuals.

Neutrophil gelatinase-associated lipocalin (NGAL) urinary was the second most frequently mentioned marker in the analyzed articles. In the study by Wang and colleagues (2013), urinary NGAL was found to be 5 to 10 times higher in normo or microalbuminuric patients compared to healthy controls, suggesting that urinary NGAL may be a promising early marker for monitoring renal failure in type 2 diabetes patients in the short term (35, 36).

Type IV collagen appears to detect glomerular dysfunction in the normoalbuminuric stage. It is mentioned in the study by Currie and colleagues (2014), where it was described that serum and urinary levels of type IV collagen are elevated in diabetic patients, with significantly higher urinary excretion observed in normoalbuminuric diabetic patients (33).

Urinary ceruloplasmin excretion is higher in type 2 diabetic patients compared to control individuals, even in the normoalbuminuric phase (37).

Total urinary IgG excretion is higher in diabetic patients compared to control individuals, even before the development of microalbuminuria. This predicts the

development of microalbuminuria and is correlated with the progression of diffuse glomerular lesions (37).

Laminin urinary excretion is higher in non-diabetic chronic nephropathy compared to control individuals. Type 2 diabetic patients with evidence of nephropathy showed a significantly higher laminin/albumin ratio compared to patients with non-diabetic nephropathy, suggesting that laminin urinary excretion could help differentiate nephropathy in diabetic and non-diabetic individuals (22).

Immunoglobulin M (IgM), present in type 2 diabetic patients with macroalbuminuria, is associated with severe glomerular capillary wall injury in patients requiring renal replacement therapy and has a higher cardiovascular mortality rate (22).

Some biomarkers mentioned in Table 1 were cited in only one article, such as alpha 2-zinc glycoprotein, laminin, and lipocalin-type prostaglandin D2 synthase (L-PGDS), while others, such as Immunoglobulin M (IgM), beta 2 microglobulin, fibronectin, cystic fibrosis transmembrane conductance regulator (CFTR), Cl^-/H^+ exchanger (CIC-5), and osteopontin, appeared in two articles. This does not imply that they are less significant markers, but rather that they require more scientific investigation to be better understood (7, 22, 23, 38).

The development of this work provides a reflection on a topic of extreme importance for global health, which highlights a significant increase in CKD, particularly emphasizing the high rate of deaths associated with this comorbidity. It is also crucial to highlight the high costs related to this disease and the significant representation of expenses associated with its treatment. This underscores the importance of focusing on prevention and early diagnosis (39, 40).

This context raises concerns about early identification of CKD, aiming to treat it to mitigate and delay its effects. The study clearly and objectively highlights the connection between Diabetes Mellitus (DM) and CKD, emphasizing the importance of early disease identification (41).

Urinary albumin received attention as a consolidated marker of kidney injury in diabetic individuals, being widely used in clinical practice. On the other hand, urinary transferrin was highlighted as a comparative experimental marker.

Transferrin was identified as a more sensitive experimental marker for glomerular and/or proximal tubular damage in diabetic patients, as indicated by theoretical analysis and experimental results mentioned in the articles analyzed in this study.

Urinary transferrin excretion showed a significant linear relationship with urinary albumin excretion in diabetic patients. Furthermore, increased urinary transferrin excretion has the potential to predict the development of microalbuminuria in type 2 diabetic patients who initially present normoalbuminuria (22, 42). These findings suggest that urinary transferrin may be a more sensitive indicator for early detection of DN than microalbuminuria. However, it is important to note that, like albumin, urinary transferrin excretion may also be elevated in other conditions affecting the glomerulus, such as primary glomerulonephritis (16, 22, 32, 43).

Wang's group (2013) confirmed this finding and described that urinary transferrin excretion is not specific to diabetic kidney disease and is also increased in primary glomerulonephritis (35).

Studies by Al-Rubeaan et al. (2017) and Bucay et al. (2012) highlighted that increased urinary transferrin excretion precedes the increase in urinary albumin excretion in diabetic patients (22, 32).

In a study using a type 1 DM animal model, Figueira and colleagues (2017) showed that urinary transferrin excretion was twice as high compared to control animals, suggesting dysfunction in the proximal tubular endocytosis machinery (7).

The involvement of the proximal tubule in diabetic proteinuria has become a focus of interest in recent years. Different studies show that changes in patterns of urinary protein excretion originate not only in the glomeruli, as previously believed, but also in the proximal tubule. These results provide crucial information about the critical role of the proximal tubule in the pathophysiology of diabetic nephropathy, highlighting an important pathway for the future development of tools for the diagnosis and intervention in the course of diabetic kidney disease (7).

CONCLUSIONS

Here, the need to understand the relationship of urinary transferrin as an experimental marker of renal injury in diabetic patients was demonstrated, drawing the attention of physicians and other healthcare professionals involved in this care, highlighting the importance of appropriate treatment, initial approach, and care and prevention measures for diabetic kidney disease (DKD).

This study makes it clear the need to define a standardized way of quantifying urinary transferrin, through a laboratory kit with established values for comparative analysis of urinary transferrin with albuminuria and other markers under study.

The present study demonstrates the need in clinical practice to identify new biomarkers with potential for early diagnosis and risk stratification and monitoring of patients with DKD.

This work also demonstrated the need to better understand the relationship of transferrin as a laboratory marker of renal injury in patients with DM and to evaluate in a larger group of patients in the 5 stages of kidney disease, including patients on renal replacement therapy, to follow these patients from the onset of the disease and when renal transplants are performed.

It is necessary to develop new diagnostic methods to implement transferrin as a clinical tool in the early diagnosis of DKD.

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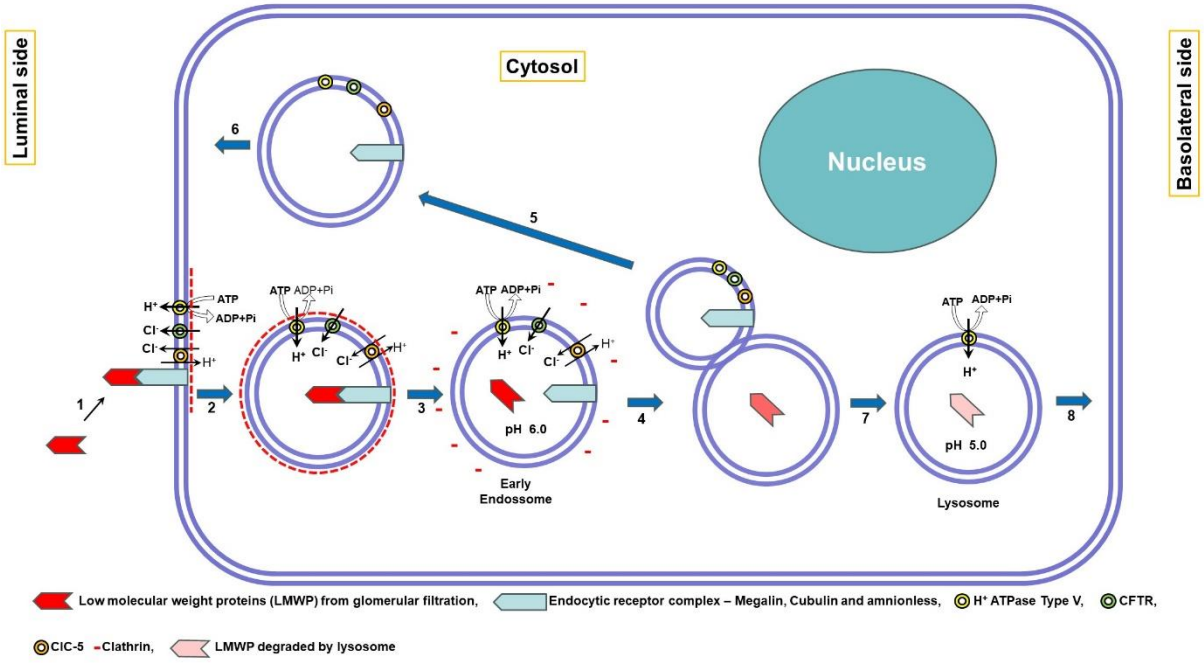

Figure 1 – Schematic view of the endocytosis process described in renal proximal tubules. Observe the important roles of H+-ATPase, ClC-5, and CFTR in the steps involved in endosomal acidification:

1 – Binding of Low Molecular Weight Proteins (LMWP) to the megalin/cubilin complex. 2 – Internalization of LMWP bound to the megalin/cubilin complex. 3 – Formation of the primary endosome and endosomal acidification by H+-ATPase type V activity, regulated by CFTR and ClC-5. At this step, the LMWP unbind from the megalin/cubilin complex. 4 – Formation of recycling and lysosomal vesicles. 5 and 6 – Recycling of the endocytic apparatus to the luminal membrane. 7 – LMWP follows the lysosomes. 8 – Degraded LMWP are exocytosed to the basolateral membrane. Here, only H+-ATPase type V, megalin/cubilin, ClC-5, and CFTR are represented; for simplicity, other membrane proteins of the endocytic apparatus are not shown.

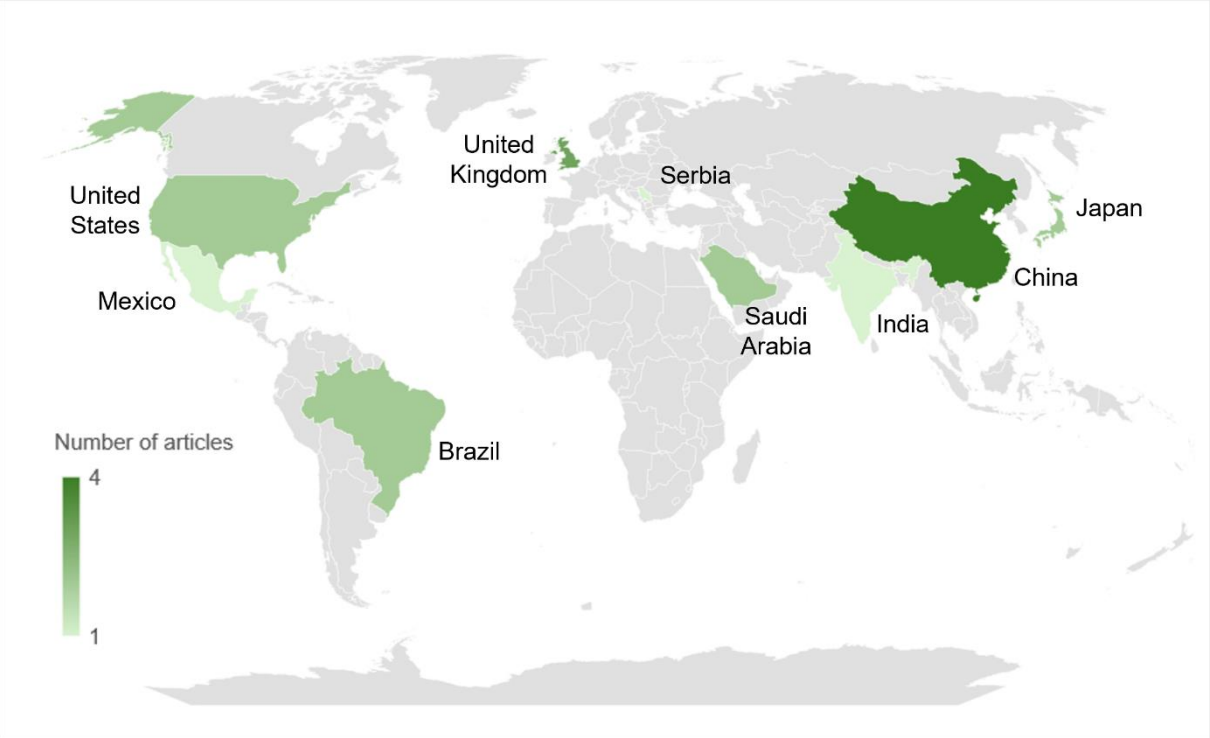

Figure 2 – Geographic distribution of the publications. Note that the American continent contributed with 10 articles selected in the present review, approximately 55%.

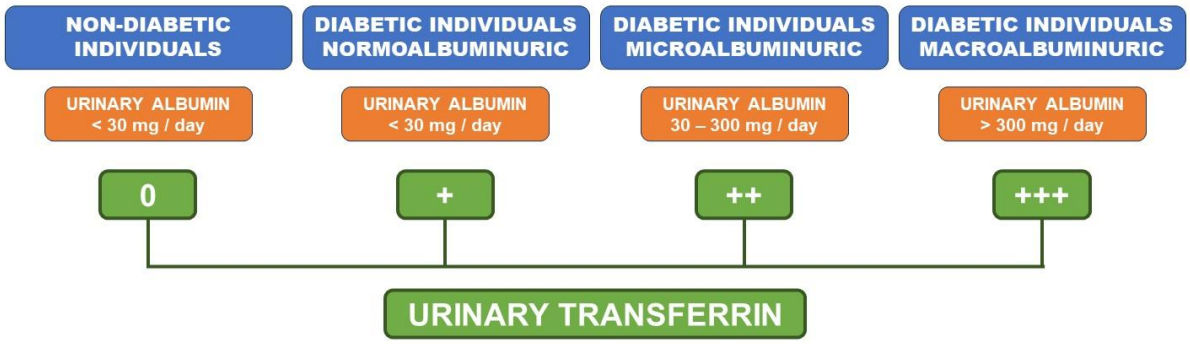

Figure 3 – Representative scheme of the relationship between urinary albumin and transferrin in non-diabetic and normo, micro, and macroalbuminuric diabetics individuals. 0 = no transferrin detection. + = mild transferrin detection. ++ = moderate transferrin detection. +++ = high transferrin presence.

Table 1 – Urinary markers of kidney injury.

Markers	Year										
	2002	2003	2004	2012	2013	2014	2015	2017	2019	2020	2021
Glomerular Damage											
Albumin	+	+	+	+	+	+	+	+	+	+	+
Transferrin	+	+	+	+	+	+	+	+	+	+	+
Fibronectin				+			+				
Human ZINC-α (2) – Glycoprotein Urinary					+						
IgM				+	+						
Laminim				+							
L-PGDS				+							
MCP-1					+					+	
Type IV Collagen				+	+		+				
Tubular Damage											
CFTR								+			
CIC - 5								+			
Cubilin							+	+			
Cystatin C					+		+				
GAGS				+			+				
KIM - 1							+			+	
Megalin							+	+			
NAG				+			+				
NGAL					+	+	+	+		+	
RBP						+		+		+	
Urinary B2 Microgobulin	+						+				
Podocyte Damage											
Urinary Podocalyxin					+		+				
Oxidative stress and inflamation											
Ceruloplasmin			+	+	+						
Interleukin - 6								+			
8 - OXODG					+		+				
PP											
IgG4			+	+							
IgG			+	+	+						
Others											
Urinary Proteomics					+		+			+	
Urinary Osteopontin*					+						

CFTR: Cystic Fibrosis Transmembrane Conductance Regulator. **GAGS**: Glycosaminoglycans. **IgG**: Immunoglobulin G. **IgG4**: Immunoglobulin G4. **IgM**: Immunoglobulin M. **KIM-1**: Kidney Injury Molecule 1. **L-PGDS**: Lipocalin-type Prostaglandin D2 Synthase**. MCP-1**: Monocyte Chemoattractant Protein-1. **NGAL**: Neutrophil Gelatinase Associated Lipocalin. **RBP**: Urinary Retinol Binding Protein. **PP**: Plasma Proteins. **Urinary Proteomics**: Alpha-2 Glycoprotein, Alpha-1 Acid Glycoprotein, Alpha-1 Microglobulin and IgG. **8-OXODG**: 8-Oxo-7,8-Dihydro-2'-Deoxyguanosine
*Present in rats.