



Glomerulonephritis in schistosomiasis mansoni: a time to reappraise

Glomerulonefrite na esquistossomose mansônica: um tempo para reavaliar

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ABSTRACT

Introduction: The current prevalence of glomerulonephritis in patients with hepatosplenic schistosomiasis mansoni in Brazil was evaluated. **Methods:** Sixty three patients (mean age 45.5±11 years) attending the outpatient infectious disease clinic of a University Hospital in Belo Horizonte, Brazil, from 2007 to 2009, were consecutively examined and enrolled in the present investigation. Diagnosis of hepatosplenic schistosomiasis was based on epidemiological, clinical and parasitological data and imaging techniques. Eight patients, who presented >30mg/day albuminuria, were submitted to percutaneous ultrasound guided renal biopsy. Kidney tissue fragments were examined under light, direct immunofluorescence and electron microscopy. **Results:** All patients showed mesangial enlargement. In five, mesangial hypercellularity was observed and four presented duplication of the glomerular basement membrane. Areas of glomerular sclerosis were diagnosed in four. Deposits of immunoglobulin M and C3 were present in six samples; deposits of IgG in four, IgA in three and C1q in two samples. In all patients, immunoglobulin A was reported in the lumen of renal tubules. Deposits of *kappa* and *lambda* were observed in six samples. Electron microscopy revealed dense deposits in the glomerular tissue of three patients. Arterial hypertension, small esophageal varices, slight increases in serum creatinine and decreases in serum albumin were associated with glomerular disease. **Conclusions:** Renal disease associated with hepatosplenic schistosomiasis was verified in 12.7% of patients and type I membranoproliferative glomerulonephritis was observed in 50% of them. Schistosomal glomerulopathy still is an important problem in patients with hepatosplenic schistosomiasis in Brazil.

Key-words: Schistosomiasis. Schistosomal glomerulopathy. Glomerulonephritis. Histopathology.

RESUMO

Introdução: Avaliou-se a frequência de glomerulonefrite em pacientes com esquistossomose hepatosplênica no Brasil. **Métodos:** Selecionou-se para o estudo, 63 pacientes (idade média de 45,5±11 anos) avaliados consecutivamente no ambulatório de doenças infecciosas de um hospital universitário de Belo Horizonte, Brasil, no período de 2007 a 2009. O diagnóstico da esquistossomose foi baseado em dados epidemiológicos, clínicos, parasitológicos e de imagem. Os oito pacientes que apresentaram albuminúria acima de 30mg em 24 horas submeteram-se a biópsia renal percutânea dirigida por ultrassonografia. As amostras de tecido renal foram analisadas à microscopia óptica, eletrônica e de fluorescência direta. **Resultados:** Havia expansão do mesângio em todos. Em cinco, houve proliferação de células mesangiais e em quatro observou-se duplicação da membrana basal glomerular. Áreas de esclerose glomerular foram diagnosticadas em quatro. Depósitos de imunoglobulinas M e C3 foram presentes em seis amostras; IgG em quatro, IgA em três e C1q em duas. Em todos os pacientes relatou-se fluorescência para IgA dentro dos túbulos renais. Depósitos de *kappa* e *lambda* foram vistos em seis amostras. A microscopia eletrônica demonstrou depósitos eletrondensos em tecido glomerular. A presença de hipertensão arterial, varizes do esôfago de pequeno calibre, pequenos aumentos de creatinina e diminuição de albumina sérica associaram-se à ocorrência de dano renal. **Conclusões:** A frequência de lesão renal foi de 12,7%, no presente estudo, e a glomerulonefrite membranoproliferativa do tipo I foi encontrada em 50%. A lesão renal associada à esquistossomose permanece um problema importante no Brasil.

Palavras-chaves: Esquistossomose. Nefropatia esquistossomótica. Glomerulonefrite. Histopatologia.

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INTRODUCTION

It has been estimated that 3.5% of the world's population (200 million people) is infected with the 3 main species of *Schistosoma* (*mansoni*, *haematobium* and *japonicum*). The disease causes 200 thousand deaths in sub-Saharan Africa each year. In Brazil, 42 million individuals live in endemic areas and 6 million are infected with *Schistosoma mansoni*^{1,2}. Renal involvement in schistosomiasis is an important cause of end-stage renal disease and increases the socioeconomic impact of schistosomiasis³⁻⁵.

No consensus has been achieved regarding the prevalence of renal disease in schistosomiasis. Studies in Brazil show that up to 15% of patients with hepatosplenic schistosomiasis also present renal disease⁶⁻¹⁴. In Egypt, Barsoum^{15,16} reported that in 10% of patients on chronic hemodialysis, schistosomiasis was the primary cause of their renal failure. In Brazil, in the late sixties, Andrade and Queiroz⁵ detected glomerular lesions in 9 (45%) out of 20 patients with hepatosplenic schistosomiasis in an autopsy series. Another study in Brazil revealed a prevalence of glomerulonephritis associated with hepatosplenic schistosomiasis of 15%⁸ in a nephrology reference center. In field-works, using proteinuria as a marker of renal disease, the prevalence varied from 6% to 15%^{7,9,11}.

In a more recent and instigating review, Andrade¹⁷ suggested that renal disease associated with schistosomiasis was decreasing in Brazil after mass chemotherapy for schistosomiasis was initiated in the late seventies. Since then, over 13 million treatments/re-treatments were undertaken in the country^{4,18-22}.

The present study was devised to update the current prevalence of renal disease in patients with hepatosplenic schistosomiasis who attended a reference center for schistosomiasis of an University Hospital of the Southeast of Brazil, from 2007 to 2009.

METHODS

Patients

This is a cross-sectional study. All patients with hepatosplenic schistosomiasis mansoni attending the reference center for schistosomiasis of the

Federal University of Minas Gerais, in Brazil, from February 2007 to January 2009, were consecutively selected for this investigation. The study was approved by the Human Research Ethical Board of the School of Medicine of the Federal University of Minas Gerais. Sixty-six patients provided written informed consent to participate and were examined; however, three were excluded during the initial diagnostic procedures (one coinfecting with hepatitis C virus) or during follow-up (one refused to continue the required tests and one moved to another city). Therefore, 63 patients, 46 (73%) male, in the age range of 34 to 56 years-old (mean of 45.5 ± 11), were followed until the completion of the laboratory tests.

In **Figure 1**, the origins of the 63 patients with hepatosplenic schistosomiasis are depicted. Most of them came from the State of Minas Gerais.

Diagnosis of hepatosplenic schistosomiasis

Diagnosis was based on: epidemiological evidence, contact with stream water from endemic areas; clinical evidence, hepato and splenomegaly; portal hypertension, esophageal varices diagnosed during upper digestive endoscopy; imaging techniques, showing significant portal vein collaterals, *S. mansoni* eggs in the stools; and ultrasound or magnetic resonance imaging, showing the characteristic Symmers' fibrosis of the liver²¹⁻²⁴. All patients had three negative parasitological stool examinations by the Kato-Katz technique and they also reported previous treatment for schistosomiasis ranging from 2 to 5 years before being enrolled in the present investigation.

Clinical examination

Clinical examination was performed by one author (VLR). Arterial blood pressure was measured on 2 different occasions (one week apart) by the same physician following the protocol established by the Brazilian Consensus on Systemic Arterial Hypertension²⁵. Patients were then instructed on the correct way of collecting a 24h urine specimen. In the second visit to the outpatient clinic, 10ml of venous blood was obtained and stored for laboratory tests.

Laboratory studies

Routine laboratory tests were performed, including a hemogram (counter *Sysmex*, E 2100 D), coagulation tests, liver function (AST, ALT, alkaline phosphatase, bilirubin, serum albumin) and renal function tests (BUN, serum creatinine). Antibodies against hepatitis C (anti-HCV) and B (HbsAg and anti-Hbc) were tested. Autoimmune diseases were also investigated: antinuclear antibodies (ANA), protoplasmic-staining antineutrophil cytoplasmic antibodies (p-ANCA) and antineutrophil cytoplasmic antibodies (c-ANCA) were measured by an indirect immunofluorescent method and anti-thyroglobulin antibodies were determined. Fasting glycemia and glycohemoglobin were measured. Venereal disease research laboratory (VDRL) was measured by a flocculation test. Serum ASTO and rheumatoid factor were also investigated.

Renal function

After 12h of oral liquid restriction, an early morning urine sample was collected in a sterile recipient. Part of the urine was seeded in a culture medium for microbiological study. Using another sample, after centrifugation, abnormal elements were investigated in the urine under light microscopy (amplification 400X). One blood cell in male centrifuged urine was considered abnormal and 3 or more in the female samples. The presence of acanthocytes and codocytes (G1 cells) defined the presence of erythrocyte dysmorphism. Dysmorphic cells were investigated by phase-contrast microscopy.

Proteinuria was measured in a 24h urine sample. Whenever the qualitative test was positive, the sulfosalicylic acid technique was used or an immunoenzymatic test was performed. Albuminuria $>30\text{mg/day}$ was considered abnormal.

Renal function was evaluated by calculating the glomerular filtration rate (GFR) according to the MDRD (Modification of Diet in Renal Disease) formula: $\text{GFR} = 170 \times \text{serum creatinine}^{-0.999} \times \text{age}^{-0.176} \times [0.762 \text{ if female}] \times \text{BUN}^{-0.170} \times \text{albumin}^{+0.318}$. The serum creatinine used in the formula was measured by a colorimetric method.

Serum complement, cryoglobulins and immunoglobulins

Serum C3 and C4 levels were quantified by nephelometry. The presence of cryoglobulins was investigated by placing the serum sample in 4°C for 72h and observing the formation of a precipitate which disappeared after heating. Serum immunoglobulin A was measured by nephelometry after the addition of specific anti-sera and the results expressed in mg/dL .

Renal biopsy

All patients with evidence of renal involvement were submitted to percutaneous ultrasound guided kidney biopsy, following a routine proposed by Quintino de Lima e Barros²⁶. The following findings were considered evidence of renal disease: albuminuria $>30\text{mg/day}$, hematuria with G1 cells and/or erythrocyte casts.

Exclusion from the study

Patients with visceral leishmaniasis, viral hepatitis C or B, HIV seropositivity, diabetes mellitus, autoimmune diseases, sickle-cell disease, primary cryoglobulinemia, Henoch-Schönlein purpura, visceral abscesses and neoplasias were excluded from the study.

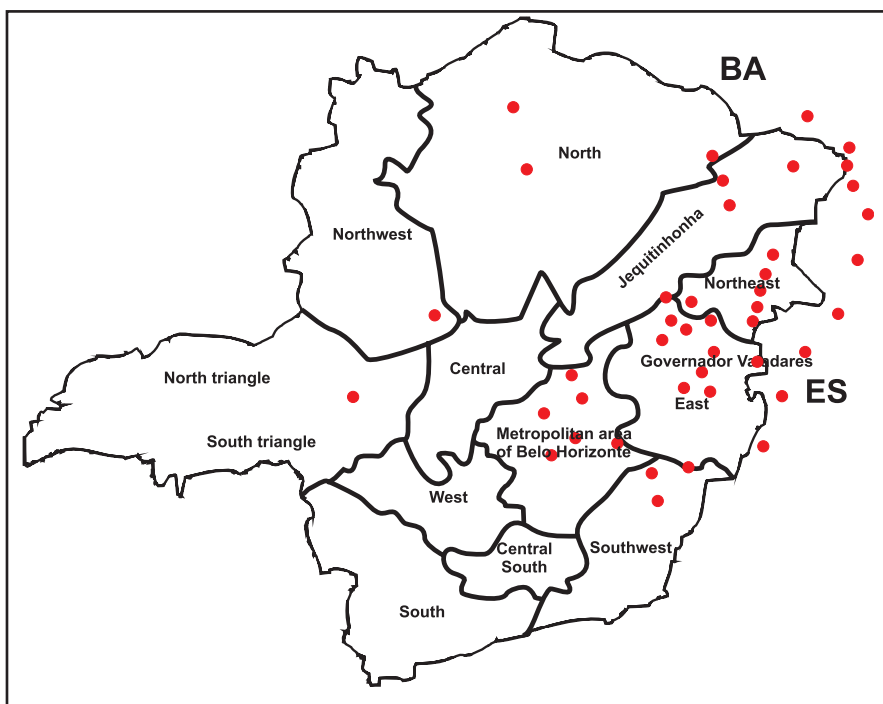


FIGURE 1 - Origin of the patients with hepatosplenic schistosomiasis. One red ball may represent more than one patient. There are cases from Bahia (BA) and Espírito Santo (ES).

Histopathology of kidney fragments

Three fragments were obtained by kidney biopsy. One was stored in 10% formaldehyde for light microscopy. Another was frozen in liquid nitrogen for immunofluorescence and a third fragment was stored in 2.5% glutaraldehyde for electron microscopy. All the samples were sent to the Department of Pathology of the Triângulo Mineiro Faculty of Medicine for processing and examination.

For light microscopy the fragments were embedded in paraffin and 2µm thick sections were cut on a microtome and stained with hematoxylin and eosin, Masson's trichrome, silver methenamine and picosirius. For immunofluorescence, fragments embedded in tissue tech were cut to 2µm thickness on a cryostat and investigated for deposits of IgA, IgG and IgM, *kappa* and *lambda* light chains and complement C1q and C3 and fibrinogen. For electron microscopy the tissue was fixed in Trump's fixative then routinely processed into resin embedded blocks; ultrathin sections were stained with uranyl acetate and lead citrate and examined with a Philips CM100 transmission electron microscope.

Statistical analysis

Data from questionnaires were transferred to a databank using EpiData 3.1 (EpiData Association, Odense, Denmark) and analyzed by the *Statistical Package for Social Sciences* (SPSS) 12.0 (SPSS inc., IBM Company, Chicago, Illinois). As a first step, descriptive analysis (frequency tables and exploratory data analysis for qualitative and quantitative variables, respectively) was performed. Cases and controls were compared using the Chi square or Fisher exact (qualitative variables) and Mann-Whitney (quantitative variables) tests. Logistic regression models were performed to identify risk factors associated with renal disease. To enter variables in the model, a *p* value of 0.2 was used. To remain in the final model, a *p* value of 0.05 was adopted. Odds ratios (OR) and 95% confidence intervals (95%CI) were estimated. Model adjustment was tested by goodness of fit using the Hosmer & Lemeshow technique²⁷.

Ethical aspects

The present investigation was approved by the Human Research Ethical Board of the School of Medicine of the Federal University of Minas Gerais.

RESULTS

Sociodemographic and clinical characteristics

Forty-six (73.0%) out of 63 patients were male, with a mean age of 45.5±11 years-old. The mean weight was 65.7kg (±11.9) and the mean height was 164.9cm (±8.5). The mean BMI was 24.1kg/m² (±3.5) and mean body surface area was 1.7m² (±0.2). Clinical data for the 63 patients are shown in **Table 1**. The mean systemic blood pressure was significantly higher in patients with renal disease than in controls (*p*=0.03). A patient with hypertension was 8 times more likely to present renal disease. Small sized esophageal varices were more common in the group with renal disease (*p*=0.02).

Laboratory tests

Antinuclear antibodies (ANA) were detected in 6 (9.5%) out of 63 patients at titers <1:160. Rheumatoid factor was present in 16 (25.4%), cryoglobulinemia in 3 (4.8%), p-Anca in 3 (4.8%), C3 levels were consumed in 21 (33.3%) and C4 in 29 (46%). Serum protein electrophoresis revealed polyclonal hypergammaglobulinemia (>1.5g/dL) in 40 (63.5%) patients. No significant differences were observed between the groups with and without renal disease for the above tests.

TABLE 1 - Clinical data of 63 patients with hepatosplenic schistosomiasis.

Clinical data	Patients (n = 63)	
	number	percentage
Spleen		
palpable	48	77.2
splenectomized	15	22.8
Esophageal varices*		
small	13	20.6
medium	25	39.7
large	26	39.7
Hepatomegaly		
left lobe increase	19	30.2
diffuse increase	22	34.9
non palpable	22	34.9
Digestive bleeding		
yes	41	65.1
no	22	34.9
Systemic arterial blood pressure (mmHg)		
mean**	SBP=127.6±20.7 DBP=78.8±11.5	

*diagnosed by upper digestive endoscopy, **mean of 63 patients, SBP: systolic blood pressure, DBP: diastolic blood pressure.

Findings in urine

None of the patients presented glycosuria, or bilirubinuria and culture of urine specimens for bacteria were negative. Seven (11.1%) patients presented hematuria and 8 (12.7%) presented proteinuria. Patients with increased proteinuria were considered to have renal disease. In the 24h urine specimens, the measured creatinine and the expected creatinine were both calculated using the modified *Cockcroft-Gault* formula: [(140-age) x ideal weight x 0.2] x 0.85 for women, and was always superior to 0.85, validating other urinary solutes measured.

Kidney histology

Mesangial injury was reported in all 8 biopsy specimens examined. In 2 cases, only mesangial expansion was observed and in 6, mesangial expansion and cell proliferation were observed. Duplication of the glomerular basement membrane of the capillary walls was revealed in 4 cases. In 3 fragments, segmental glomerular sclerosis was reported and in one, the sclerosis affected more the 50% of the glomeruli (diffuse involvement). Deposits of immunoglobulins were observed in most fragments (87.5%); IgG in 50%, IgM in 63% and IgA in 38%. The C3 fraction of complement was reported in 75% and C1q in 2 samples. In renal tubules, around tubular casts, deposits of IgA were observed in all cases and *kappa* and *lambda* chains in 75%. Electron-dense deposits were observed in the glomerular structure of 3 patients; all with type I membranoproliferative glomerulonephritis (**Figure 2**).

The final histopathological diagnoses were: type I membranoproliferative glomerulonephritis in 4 patients; mesangioproliferative with segmental sclerosis and deposits of C3 in one patient; mesangial with deposits of IgA, C1q and C3 in one patient; mesangial with segmental sclerosis and deposits of IgM, C3 and C1q in one patient; and mesangial glomerulonephritis with deposits of IgM, IgG and IgA in one patient.

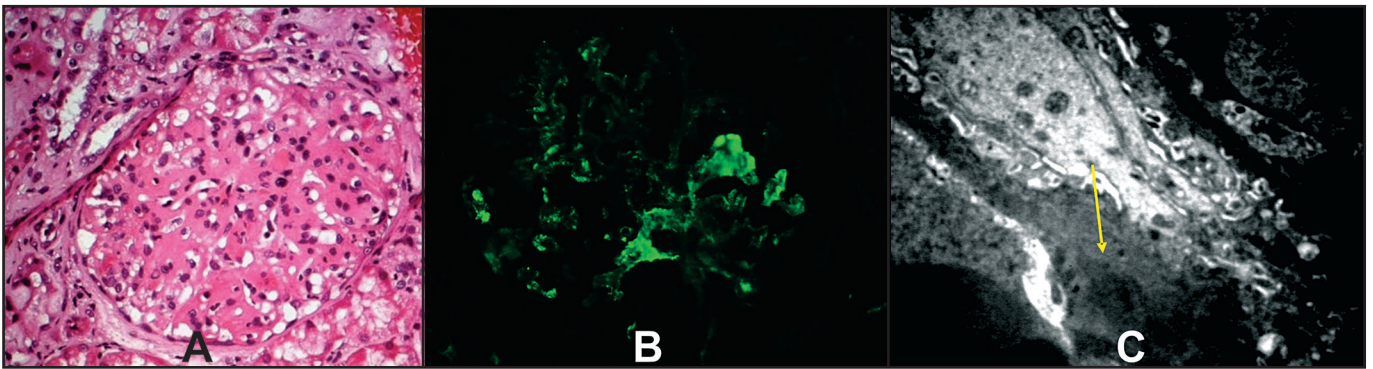


FIGURE 2 - A). Optic microscopy of a patient with type I membranoproliferative glomerulonephritis; B). Immunofluorescence showing IgG deposits in the glomerular structure of a glomerulus; C). Electron microscopy showing electron dense deposits (arrow) in the basement membrane of a glomerulus.

DISCUSSION

Eight (12.7%) out of 63 patients presented evidence of glomerular involvement. In 4, a diagnosis of type I membranoproliferative glomerulonephritis was confirmed. These findings are similar to those previously described and do not support a decrease in the frequency of renal disease in hepatosplenic schistosomiasis reported by others¹⁷.

The most common clinical evidence of renal involvement in the present cases were systemic arterial hypertension, edema, proteinuria and glomerular hematuria. Nephrotic syndrome (proteinuria over 3.5g/day) was reported in 4 (50%) out of 8 patients with renal disease and, in all, hematuria and low serum levels of C3 were present. In one patient, renal biopsy was performed because he had proteinuria of 73.6mg/day and a very low serum level of the C3 component of complement; renal disease was confirmed by kidney biopsy. Therefore, even minor alterations in the urine of patients with hepatosplenic schistosomiasis, should be investigated by the attending physician.

A curious finding was the association of esophageal varices of small caliber and the presence of renal disease. We postulated that patients with large esophageal varices died earlier (digestive bleeding) and, consequently, older people (those with small varices) would have survived longer and had a greater chance of developing renal injury. However, no age difference was determined between groups with different varix sizes. Another hypothesis was that patients with smaller varices had large spontaneous portal shunts (*porta-cava* communication) deviating blood from the varices and redirecting blood antigens to the kidney (still to be evaluated). The present findings must be confirmed by others. It is important to emphasize that the size of varices is based on the subjective evaluation of the endoscopy examiner.

Nearly one third of the patients presented a decrease in the serum levels of the C3 and C4 components of complement and the consumption of complement was not related to kidney damage. The subject has been documented by others and its pathogenesis and importance in glomerular disease is disputed²⁸. Madwar et al²⁹ were the first to demonstrate persistent low levels of complement and its association with immune-complexes in schistosomiasis. Since only a small number of patients develop glomerulonephritis in the presence of circulating immune-complexes and complement consumption (70% of the cases), it is been suggested that some patients present what has been called *nephritogenic* immune-complexes³⁰. More recently, Skelly³¹ revealed the existence of receptors for C2, C3, C8, C9 and Fc on the surface of the schistosome; the worm blocking the complement cascade would be avoiding its own destruction by the host's immune system.

In 16 (25.4%) patients, rheumatoid factor was increased in serum (>20IU/mL), but it was not higher in those with glomerulonephritis. Some authors have reported lower serum levels of rheumatoid factor in patients with schistosomal glomerulonephritis³²⁻³⁴. The results obtained here do not support previous reports. The presence of autoantibodies in this study may be explained by the nonspecific increase in gamma globulin observed and reported in chronic diseases, such as hepatosplenic schistosomiasis and visceral leishmaniasis; there is no evidence that autoantibodies, usually in low titers, have any influence on the pathogenesis of these diseases.

The immunofluorescence study on kidney fragments of the patients did not show any singular pattern, probably reflecting different stages of glomerular damage. The suggestion by Egyptian researchers³⁵ that immunoglobulin A plays an important role in the aggravation of renal lesion in schistosomiasis, mediated by IL-6 and IL-10, was not confirmed in here. Serum levels of IgA were within normal range in all patients. In Egypt, the association of schistosomiasis with hepatitis C has been reported and the influence of the viral infection in the pathogenesis of the glomerulonephritis cannot be underestimated.

IgA was present in the glomerular structure of 2 patients. In one, mesangial expansion was also present, which might suggest a diagnosis of Berger's nephropathy (primary IgA nephropathy).

However, deposits of C1q, a product of the classic complement pathway that does not occur in IgA nephropathy, were also verified. In the second case, together with IgA, deposits of IgM, IgG and C3 were also observed. IgM deposits are not expected in Berger's nephropathy (also known as IgG-IgA nephropathy)³⁶. Glomerular deposition of IgA is also common in patients with liver cirrhosis and it has been explained by impairment in the depuration of immunoglobulins by Kupffer cells³⁷. More recently, it has been shown that the IgA deposited in Berger's nephropathy is structurally abnormal (sub-galactosylated molecules) and that it is possible to investigate the structure of its molecule.

Interestingly, in all the patients, IgA was identified in renal tubules around tubular casts. Since this is not a common finding, we hypothesized that an increase in the synthesis of this immunoglobulin was occurring due to chronic inflammatory stimulation of the intestinal mucosa caused by schistosomiasis. Thus, this macromolecule (160kd) would cross a damaged glomerular capillary and find its way into the renal tubules, without having any part in the schistosomal glomerulopathy.

In conclusion, renal disease occurred in 12.7% of the patients presenting hepatosplenic schistosomiasis. In 4 patients, the disease presented with nephrotic syndrome and all 4 had type 1 membranoproliferative glomerulonephritis. Renal tubular casts

surrounded by IgA were observed in all cases. The importance of IgA in the pathogenesis of this nephropathy is unknown and awaits further refined studies of the molecular structure of IgAs deposited in the glomeruli.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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