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Original article

Serum and urinary galactose-deficient IgA1 as a tool for diagnosis of IgA nephropathy in pediatric patients with hematuria

Background: *IgA nephropathy (IgAN) is an immunopathologic diagnosis based on a renal biopsy. Diagnosis of IgAN may not be made in the milder cases or may be delayed until clinical manifestations are severe. We sought to assess the validity of serum and urinary galactose-deficient IgA1(Gd-IgA1) as a possible non-invasive diagnostic biomarker of IgAN.* ***Methods:*** *A cross-sectional study was conducted at Pediatric Nephrology Clinic, Children's Hospitals, Ain Shams University on 40 patients with recurrent gross glomerular hematuria diagnosed with renal biopsy and divided into two equal groups, group 1 patients with IgAN and group 2 with non-IgA glomerular diseases. Serum and urinary Gd-IgA1 levels were measured by ELISA using an anti-Gd-IgA1 monoclonal antibody (KM55). Laboratory investigations included complete blood count (CBC), erythrocyte sedimentation rate (ESR), complement 3 level in serum (C3), antinuclear antibody (ANA), anti-double strand DNA, urine protein/creatinine (UP/Cr) ratio, serum, and urinary total IgA levels (ELISA).* ***Results:*** *The study included 20 patients with IgAN, of which 13 were males and 7 were females, in addition to 20 patients with non-IgAN, of which 12 were males and 8 were females. In the IgAN group median age was 6.5 (5-9) years old. In the non-IgAN group, median age was 9 (4.5-13) years old. Serum Gd-IgA1 levels were significantly elevated in children with IgAN compared with children with non-IgA glomerular diseases (p-value 0.001). The serum Gd-IgA1 cut-off point to differentiate between IgAN and non-IgA glomerular diseases was 240 ng/ml with 75 % sensitivity and 80 % specificity and AUC 80.2%. There was no statistically significant difference between IgAN and non-IgA glomerular diseases regarding urinary Gd-IgA1 (p-value 0.08), Ptn/Creat ratio (p-value 0.055), serum and urine total IgA (p-value 0.144 and 0.288).* ***Conclusion:*** *Serum Gd-IgA1 level is higher in IgAN patients compared to non-IgA glomerular diseases, serum Gd-IgA1 may be used as a non-invasive diagnostic biomarker for IgAN patients.*

Keywords: IgA nephropathy, Serum galactose-deficient IgA1, Urinary galactose IgA1

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INTRODUCTION

IgA nephropathy (IgAN) is a common form of renal glomerular disease. The main histopathological lesion characteristic of IgAN is IgA-dominant immunoglobulin deposits, which are often localized in the renal mesangial area .[1]

The true incidence of IgAN is difficult to determine because a renal biopsy is required for diagnosis. Diagnosis of IgAN may not be made in the milder cases or may be delayed until clinical manifestations are severe enough to necessitate this invasive procedure. Up to 30 -40% of patients with IgAN progress to End Stage Kidney Disease (ESKD) by 20 years. Thus development of a reliable serologic test for the diagnosis of IgAN would be a major advance for the early detection and treatment of this condition .[2]

The pathogenesis of IgAN is related to aberrantly glycosylated IgA1 where some O-linked glycans in the hinge region contain terminal N-acetylgalactosamine (GalNAc) rather than a GalNAc-galactose structure. The galactose-deficient IgA1 (Gd-IgA1) is recognized by anti-Gd-IgA1 autoantibodies .[3] This process results in the formation of circulating immune complexes, some of which deposit in the glomerular mesangium, subsequently activating mesangial cells to proliferate and overproduce extracellular-matrix proteins and cytokines, thus inciting injury of the glomerulus.[4]

Previous studies have shown that serum Gd-IgA1 level is elevated in adults and pediatric patients with IgAN, demonstrating the severity of IgAN. These findings suggest that the measurement of serum Gd-IgA1 level may be a helpful diagnostic test and could serve as a predictor of renal outcomes in IgAN. However, proving Gd-IgA1 as a biomarker has remained controversial .[5] A fraction of Gd-IgA1 from the glomerular deposits is excreted into the urine as well, thus representing a disease-specific marker of IgAN. Urinary excretion of Gd-IgA1 discriminates patients with IgAN from patients with other proteinuric renal diseases .[6]

Furthermore, the level of urinary Gd-IgA1 is correlated with proteinuria in patients with IgAN. Urinary Gd-IgA1 thus may represent a disease-specific marker of IgAN. A novel lectin-independent method was established exploiting monoclonal antibody (KM55 mAb) for measuring serum levels of Gd-IgA1.[7]

Renal biopsy provides information regarding transient conditions and has limited ability to provide an accurate assessment of disease activity. Furthermore, even if a biopsy is performed during the early stages of IgAN, pathological findings may be inconclusive, and it may be difficult to establish a prognosis. Moreover, in patients with IgAN accompanied by mild proteinuria with mild histological lesions at the time of renal biopsy, progression of proteinuria is observed in approximately 30–40% of cases. Thus, novel non-invasive biomarkers are needed for evaluation of real-time disease activity.[8]

METHODS

Study patients

The study was conducted on 20 patients diagnosed with IgAN (group A) and 20 patients with non-IgAN as post-infectious glomerulonephritis, membranous glomerulonephritis, focal segmental glomerulonephritis, and lupus nephritis (group B). All patients presented with recurrent gross glomerular hematuria from 1 to 18 years old and diagnosed with renal biopsy were included in the study. Patients with painful hematuria or systemic causes of bleeding were excluded from the study.
Sample size justification: Using the PASS 11 program for sample size calculation and assuming an Area Under ROC curve of 0.75 for Gd-IgA1 for diagnosis of IgA nephropathy, setting power at 80% and alpha error at 0.05, a sample size of 20 cases diagnosed with IgA nephropathy and 20 cases with other causes of hematuria will be needed.

Study methods

It included full history taking with special emphasis on family history of similar conditions, anthropometric parameters were measured and pointed on Z score, and complete physical examination included weight, height, vital data especially blood pressure, puffiness of eyelids, lower limb edema and ascites.

Laboratory investigations included complete blood count (CBC) by using Sysmex XN-1000, kidney function tests automated BECKMAN COULTER AU480 analyzer, erythrocyte sedimentation rate (ESR) by Westergren method, Complement 3 level in serum by turbidimetric assay, antinuclear antibody (ANA) and anti-double strand DNA by indirect immunofluorescence (IIF) technique, albumin level, complete urine analysis for RBCs, proteins and urine protein/creatinine (UP/Cr) ratio automated BECKMAN COULTER AU480 analyzer (, serum and urinary total IgA levels measured by the double enzyme-linked immune sorbent assay (ELISA) and Serum and urinary levels of Gd-IgA1 measured by ELISA technique (Bioassay Technology Laboratory, 1008 Junjiang Inter. Bldg. 228 Ningguo, Shanghai, China).

Statistical Analysis

The collected data was revised, coded, tabulated, and introduced to a PC using Statistical Package for Social Science (SPSS 15.0.1 for Windows; SPSS Inc., Chicago, IL, 2001). Data was presented and suitable analysis was done according to the type of data obtained for each parameter. Descriptive statistics included Mean and Standard deviation for quantitative parametric data, Median and Interquartile range for quantitative non-parametric data, and frequency and percentage were used for presenting qualitative data. Analytical statistics including the Student T Test was used to assess the statistical significance of the difference between the study groups' means, and the Chi-Square test was used to examine the relationship between two

qualitative variables. P-value > 0.05 will be considered statistically significant. Correlation analysis (using Pearson's method) was done to assess the strength of association between two quantitative variables. The correlation coefficient denoted symbolically ″r″ defines the strength (magnitude) and direction (positive or negative) of the linear relationship between two variables, as r = 0-0.19 is regarded as a very weak correlation, r = 0.2-0.39 as a weak correlation, r = 0.40-0.59 as moderate correlation, r = 0.6-0.79 as strong correlation, and r = 0.8-1 as very strong correlation.

RESULTS

This cross-sectional study was conducted at the Pediatric Nephrology Clinic, Children's Hospitals, Ain Shams University from June 2022 until December 2022**.**

The study included 40 patients of which 15 were males and 25 were females with median age was 7 (4.5 - 12) years old. Regarding laboratory results of the studied group, the median Ptn/Creat ratio was 0.25 (0.1 – 0.76), median serum Gd-IgA1 215 (115 - 435) ng/ml, median urinary Gd-IgA1 was 240 (170 – 440) ng/ml, serum total IgA was high in 25% of patients, and urinary total IgA was high in 27.5% of patients (table 1)**.**

According to renal biopsy findings, 50% of patients were diagnosed with IgAN, 7.5% were diagnosed with post-infectious GN, 10% were diagnosed with membranous GN, 7.5% of patients were diagnosed with focal-segmental GN, and 25% of patients were diagnosed with lupus nephritis .

The results of the current study showed that there was no significant difference between IgAN and non-IgA glomerular diseases regarding age (p-value 0.328), and regarding sex (p-value 0.744)**.**

This study showed that, by comparing between IgAN group and non IgAN group, there was a high significance in serum Gd-IgA1 in the IgAN group (p-value 0.001) and there was no significant difference regarding pts/creat ratio(p-value 0.055), urine Gd-IgA1(p-value 0.08), serum total IgA(p-value 0.144), and urine total IgA (p-value 0.288) (table 2). There was significant correlation found between serum Gd-IgA1 and urinary Gd-IgA1 (figure1). There was no significant correlation found between serum Gd-IgA1 and age, protein creatinine ratio and significant correlation between serum Gd-IgA1 and urinary Gd-IgA1 (table 3)**.**

ROC curve showed that the best cut-off value to differentiate between IgA nephropathy and non-IgA nephropathy regarding serum Gd-IgA1 was found at 240 ng/ml with a sensitivity of 75%, specificity of 80.0% and area under the curve (AUC) of 80.2% (figure. 2).

Table 1. Descriptive data of all the studied patients (n=40)

Age (years)	Median (IQR)	7 (4.5 – 12)
	Range	2 – 17
Sex	Female	15 (37.5%)
	Male	25 (62.5%)
Diagnosis	IgA Nephropathy	20 (50.0%)
	Post Infectious GN	3 (7.5%)
	Membranous GN	4 (10.0%)
	Focal segmental GN	3 (7.5%)
	Lupus Nephritis class	10 (25.0%)
Lupus nephritis class	II	1 (10.0%)
	III	5 (50.0%)
	IV	1 (10.0%)
	V	3 (30.0%)
Ptn/Creat ratio	Median (IQR)	0.25 (0.1 - 0.76)
	Range	0.02 – 7
Gd-IgA1(Serum) (ng/ml)	Median (IQR)	215 (115 - 435)
	Range	35 – 930
Gd-IgA1 (Urine) (ng/ml)	Median (IQR)	240 (170 - 440)
	Range	60 – 900
Total IgA (Serum)	Normal	30 (75.0%)
	High	10 (25.0%)
Total IgA (Urine)	Normal	29 (72.5%)
	High	11 (27.5%)

IQR = interquartile range, GN = glomerulonephritis, Ptn/Creat ratio = protein/creatinine ratio, Gd-IgA1 = galactose deficient immunoglobulin A1, IgA = immunoglobulin A

Table 2. Comparison between IgA nephropathy and non-IgA nephropathy groups regarding laboratory results of the studied patients

		IgA nephropathy	**Non-IgA nephropathy**	**P- value**
		No.= 20	**No.= 20**	
Ptn/Creat ratio	Median (IQR)	0.14 (0.08 – 0.35)	0.39 (0.17 – 0.89)	0.055
	Range	0.02 – 7	0.07 – 1.5	
Gd-IgA1(Serum) (ng/ml)	Median (IQR)	375 (230 – 515)	120 (90 – 215)	0.001
	Range	100 – 930	35 – 570	
Gd-IgA1 (Urine) (ng/ml)	Median (IQR)	300 (190 – 570)	225 (100 – 300)	0.080
	Range	90 – 900	60 – 870	
Total IgA (Serum)	Normal	13 (65.0%)	17 (85.0%)	0.144
	High	7 (35.0%)	3 (15.0%)	
Total IgA (Urine)	Normal	13 (65.0%)	16 (80.0%)	0.288
	High	7 (35.0%)	4 (20.0%)	

IQR = interquartile range, Ptn/Creat ratio = protein/creatinine ratio, Gd-IgA1 = galactose deficient immunoglobulin A1, IgA = immunoglobulin A

Table 3. Correlation of Gd-IgA1 in serum and urine with the other studied parameters

	Gd-IgA1(Serum) (ng/ml)		**Gd-IgA1 (Urine)** (ng/ml)	
	R	**P- value**	**r**	**P- value**
Gd-IgA1(Serum) (ng/ml)			**0.343***	**0.030**
Gd-IgA1 (Urine) (ng/ml)	**0.343***	**0.030**		
Age(years)	0.067	0.679	-0.199	0.219
Height / Length (z score)	-0.035	0.832	-0.049	0.765
Weight (z score)	0.082	0.613	-0.163	0.314
Systolic BP (Z score)	-0.155	0.340	-0.210	0.193
Diastolic BP (Z score)	-0.021	0.899	0.041	0.800
Ptn/Creat ratio	-0.024	0.882	0.014	0.929

Spearman correlation coefficient. Gd-IgA1 = galactose deficient immunoglobulin A1, BP = blood pressure, Ptn/Creat ratio = protein/creatinine ratio

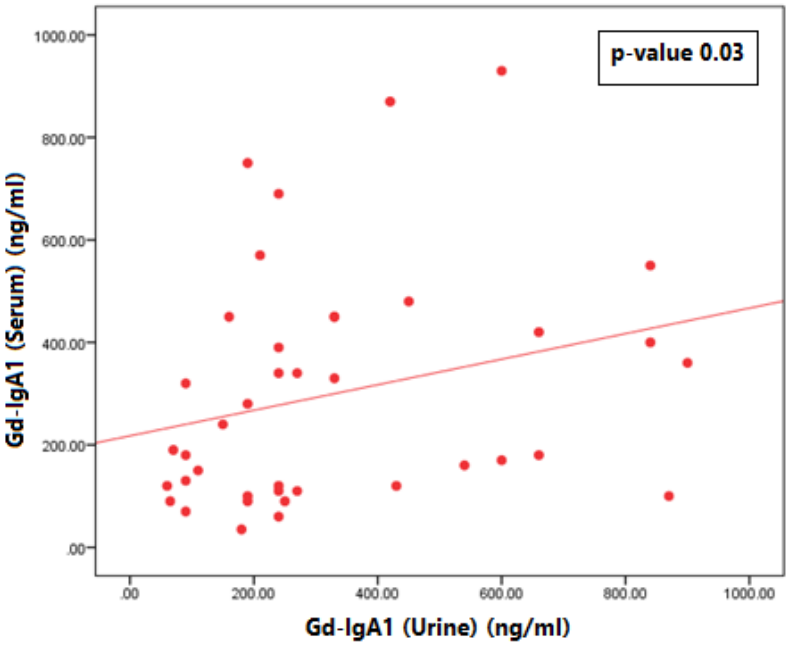

Figure 1. Positive correlation of Gd-IgA1 in serum and urine

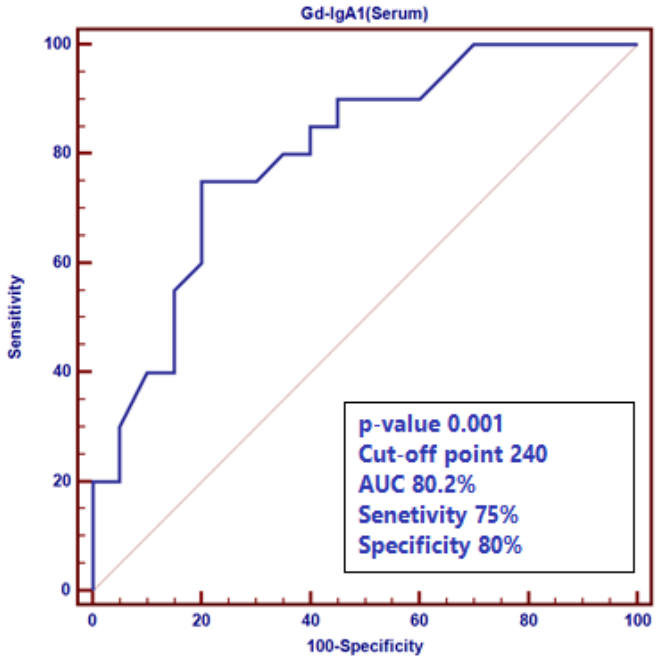

Figure 2. ROC between IgA nephropathy and non-IgA nephropathy regarding serum Gd-IgA1

DISCUSSION

IgAN is one of the causes of primary glomerulonephritis and often presents with urinary abnormalities, such as microscopic hematuria and low-grade proteinuria .[9] Based on the multihit pathogenesis of IgAN, immune complexes formed by the binding of Gd-IgA1 by Gd-IgA1-specific IgG or IgA in the circulation deposit in the mesangium and activate resident cells .[6] Activated mesangial cells produce inflammatory cytokines that cause glomerular injury. These reports suggest that Gd-IgA1- containing immune complexes play an essential role in the pathogenesis of IgAN .[4]

This study was conducted and aimed to assess the value of serum and urinary Gd-IgA1 as a possible non-invasive diagnostic biomarker of IgAN compared to renal biopsy.

In this study, there was no significant difference between the IgAN group and non-IgAN group regarding age and sex, with a median age of 6.5 (5-

9) years and male predominance (65.0%) for the IgAN group. This is close to the study that done by Jiang et al., (2015) [10] who measured the serum levels of Gd-IgA1 in 72 pediatric patients with IgAN and found 79% of patients were males with a median age of 9.3 (4.1-14.1) years. As well Sanders et al., (2017) [11] who found that 69% of their patients were males with median age of 14.3 (8.6-17.2) years. Also, Irabu et al., (2020) [9] found that 51.5% of the patients were males with median age of 10.6 (6.9-14.5) years. This gender phenomenon reveals that males are more likely to be affected by the most of glomerular diseases.

Regarding the protein-creatinine ratio in this study, there was no significant difference between the IgAN group and the non-IgAN group (p-value 0.055). In agreement with Kim et al., (2020) [12] who investigated the clinical relevance of serum Gd-IgA1 levels in 230 biopsy-proven IgAN patients and 74 patients with non-IgAN. And there was no significant difference in the protein-creatinine ratio between the IgAN group and the non-IgAN group. Proteinuria is a common feature in different glomerular disorders and cannot differentiate between them but its change within a patients might reflect disease progression.

In this study, serum Gd-IgA1 was significantly higher among IgAN patients. The best cut-off points to differentiate between IgAN and non-IgAN regarding serum Gd-IgA1 were found 240 ng/ml with a sensitivity of 75%, specificity of 80.0%, and area under ROC curve of 80.2%.Our observation agree with Irabu et al., (2020) [9] who investigated the clinical significance of Gd-IgA1 levels in 33 children with IgAN with median age of 10.6 (6.9-14.5) years and 40 with non-IgA glomerular diseases, and found that serum Gd-IgA1 levels were significantly elevated in children with IgAN compared with children with non-IgAN, the reported cut-off point was 3236 ng/ml, with sensitivity 92% and specificity 81.8%. Also, Sanders et al., (2017) [11] examined serial serum Gd-IgA1 levels over 1 year in 13 children with IgAN and found that serum Gd-IgA1 levels were significantly higher in IgAN patients than non-IgAN patients. Similarly, Jiang et al., (2015) [10] measured the serum levels of Gd-IgA1 in 72 pediatric patients with IgAN. They reported that serum levels of Gd-IgA1 in children with IgAN were higher than controls of non-IgAN. The cut-off point for galactose-deficient IgA1 levels was 1250 ng/mL, with a sensitivity of 87.5% and a specificity of 83.3%.

Martín-Penagos et al., (2021) [13] and Bagchi et al (2019) [14], had similar observations as well. The difference in cut off levels between their studies and our might be related to difference in disease severity between their patients and ours, sample size difference, and the possibly the kits used. Kim et al., (2020)[12] had the same observation in the adult population as they investigated the clinical relevance of serum Gd-IgA1 levels in 230 biopsy-proven IgAN adult patients and 74 adult patients with non-IgAN and found that serum Gd-IgA1 levels were significantly higher in IgAN patients than non-IgAN patients (p-value< 0.001).

The multi-hit hypothesis of IgAN pathogenesis is widely accepted. This multi-hit hypothesis proposes the following disease pathogenesis: first, an increase in aberrant glycosylation of IgA1 leading to overproduction of Gd-IgA1; second, synthesis of antibodies that recognize Gd-IgA1; third, formation of pathogenic immune complexes; and fourth, mesangial deposition of these complexes and initiation of renal injury. Several studies have provided evidence supporting the multi-hit hypothesis, and These findings suggest that the measurement of serum Gd-IgA1 may be used as a non-invasive diagnostic biomarker for IgAN and this study conducted by Suzuki et al., (2016) [6] But this study is the first to assess the validity of serum and urinary galactose-deficient IgA1(Gd-IgA1) as a possible non-invasive diagnostic biomarker of IgAN compared to non-IgA glomerular diseases and all patients in this study presented with recurrent gross glomerular hematuria Therefore, the study did not include a healthy group.

Regarding urinary Gd-IgA1 in this study, there was no significant difference between the IgAN group and the non-IgAN group (p-value 0.08). This disagrees with the results conducted by Suzuki et al., (2016) [6] who measured levels of urinary Gd-IgA1 in 207 adult patients with IgAN and 205 adult patients with non-IgAN. found that urinary Gd-IgA1 levels were higher in patients with IgAN (p-value 0.0001). In this study, the smaller sample size might have a role in limiting the value of urinary Gd-IgA1 in discriminating between IgA and non-IgA nephropathies and we include pediatric age group only.

Concerning total serum IgA and urinary IgA in this study, there was no significant difference between the IgAN group and non-IgAN group (p-value 0.144, 0.288, respectively). This disagrees with the results of the previously mentioned study conducted by Yanagawa et al., (2014) [17] who found

that total serum IgA was significantly higher in IgAN patients than non-IgAN patients (p-value 0.001). On the other hand, Suzuki et al., (2016) [6] who found no significant difference in total urinary IgA between the IgAN group and non-IgAN group. Several factors can impact serum IgA levels, while urinary levels have been repeatedly observed to be related to IgA nephropathy and its pathological phenotypes (Tan et al, 2009) [18].

We could not find significant correlation between serum Gd-IgA1 with age. This agrees with the results of the study conducted by Martín-Penagos et al., (2021) [13] and Zhao et al., (2012) [19] who found also no significant correlation between serum Gd-IgA1 with age. This disagrees with the results of the previously mentioned study conducted by Irabu et al., (2020) [9] who investigated the clinical significance of Gd-IgA1 levels in 33 children with IgAN and 40 with non-IgA glomerular diseases in early-stage renal diseases and found that Serum Gd-IgA1 levels in children with IgAN were positively correlated with age (p<0:0001). We found no significant correlation between serum Gd-IgA1 and protein-creatinine ratio. In harmony with Martín-Penagos et al., (2021)[13] study, which found no significant correlation between serum Gd-IgA1and protein-creatinine ratio (p=0.761), also in the study conducted by Irabu et al., (2020) [9] who found no positive correlation between serum Gd-IgA1and protein-creatinine ratio (p= 0.347) and this suggested that the serum Gd-IgA1 level may play a role in differentiating IgAN from other kidney diseases but it was not associated with the severity of the disease.

In this study, we found no positive correlation between serum Gd-IgA1 with total serum IgA. This disagrees with the results of the study conducted by Irabu et al., (2020) [9], who revealed serum Gd-IgA1 levels were positively correlated with serum total IgA levels in patients with IgAN (p < 0:001). Several factors can change serum IgA levels, e.g. Infections, allergic disorders, autoimmune diseases, limiting its value in the diagnosis /follow up in patients with IgA nephropathy.

In conclusion, serum Gd-IgA1 level is higher in IgAN patients compared to non-IgA glomerular diseases, may be used as a non-invasive diagnostic biomarker for IgAN, with limited prognostic value due to lack of correlation to degree of proteinuria. This study is indeed limited by the sample size and cross-sectional design. Further wide scales studies are recommended to provide better assessment of the predictive value of urinary Gd-IgA1 in diagnosis of IgAN in pediatric patients compared to invasive renal biopsy.

AUTHORS CONTRIBUTION

IZH and **MSF** designed the study, **NLM** and **NAR** performed the study, **MSF** and **NAR** edited the results, **MSF** and **NAR** analyzed the data and wrote the draft version of the paper. Finally, **IZH** and **MSF** edited and approved the final version of the manuscript.

CONFLICTS Of INTEREST

The authors declare no conflict of interest.

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