Original Article

A Study of Oxidative Stress, Inflammation, and Endothelial Dysfunction in Diabetic and Nondiabetic Chronic Kidney Disease Pre-Dialysis Patients

Abstract

Background: Oxidative stress, inflammation, and endothelial dysfunction represent a key triad for the development and progression of atherosclerosis. Due to chronic low-grade inflammation in chronic kidney disease (CKD), concentrations of various inflammatory, endothelial, and oxidative stress markers are elevated, increasing the risk of atherosclerosis. The present study was undertaken to compare oxidative stress, inflammation, and endothelial dysfunction in diabetic and nondiabetic CKD pre-dialysis patients. **Materials and Methods:** This was an observational study on 120 CKD pre-dialysis patients: 60 with diabetes and 60 without diabetes. Markers of oxidative stress were measured in blood – malondialdehyde (MDA), ferric reducing ability of plasma (FRAP), paroxonase-1 (PON-1), ischemia-modified albumin (IMA); inflammation – interleukin-6 (IL-6), high-sensitivity C-reactive protein (hsCRP); and endothelial dysfunction – nitric oxide (NO), carotid wall intima–media thickness (CIMT). Comparisons between the two groups for continuous variables were made with the Student's unpaired *t*-test or Mann–Whitney test and for categorical values with χ^2-test, as appropriate. **Results:** MDA, IMA, IL-6, hsCRP, NO, and CIMT were significantly higher, while FRAP and PON-1 were significantly lower in the diabetic group when compared to nondiabetic group ($P < 0.001$). The number of atherosclerotic plaques was also significantly higher in the diabetic group compared to nondiabetic group. **Conclusion:** Our study showed increased oxidative stress, inflammation, endothelial dysfunction, and atherosclerosis in diabetic CKD pre-dialysis patients when compared to nondiabetic CKD pre-dialysis patients and in late stages when compared to early stages of CKD in both groups, indicating increased cardiovascular risk in late stages and diabetic CKD pre-dialysis patients.

Keywords: *Atherosclerosis, chronic kidney disease, endothelial dysfunction, inflammation, oxidative stress*

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Introduction

Cardiovascular disease risk is increased in patients with chronic kidney disease (CKD), partly by augmentation of atherosclerotic process,[1] attributed to risk factors like oxidative stress, chronic inflammatory state, anemia, anasarca, fluctuation in systemic fluid volume, coagulopathy and poor functioning platelets, malnutrition, accumulation of metabolic uremic products, calcium–phosphate metabolism disturbances, and numerous undefined toxic agents.[2] Uremic milieu produces oxidative stress[3] and carbonyl stress[4] both of which are highly proinflammatory. Metabolic acidosis is another cause of inflammation.[5] Increased production and decreased renal clearance accounts for higher levels of circulating cytokines in CKD.[6] Chronic periodontal inflammation,[7] intestinal dysbiosis,[8] and vitamin D deficiency[9] are also associated with elevation of inflammatory biomarkers. Increased levels of C-reactive protein (CRP) and other proinflammatory interleukins (IL) such as IL-1β, IL-6, and tumor necrosis factor-α (TNF-α) are strongly associated with high mortality and CVD complications.[10] IL-6 itself has atherogenic properties, showing its effects on platelets, endothelium, and coagulation factors.[11] In the general population, IL-6 and CRP have emerged as the best predictors of cardiovascular risk among proinflammatory cytokines, but their value in CKD has to be assessed.

Inflammation is associated with increased oxidative stress leading to increased levels of malondialdehyde (MDA), a water-soluble low-molecular-weight product of lipid

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peroxidation.[12] The ferric reducing ability of plasma (FRAP) assay is used as an index of antioxidant potential of body.[13] Paraoxonase-1 (PON-1) is an enzyme (calcium-dependent esterase) associated with high-density lipoprotein (HDL) subfractions that contain apo A-1 and clusterin and confers protection against oxidative damage of various cells and low-density lipoprotein [LDL]. Changes in HDL subfractions may cause reduction of PON-1 activity.[14]

Ischemia-modified albumin (IMA) is formed by modification of albumin (ALB) during ischemia due to hypoxia or free radical damage or acidosis in CKD.[15] CKD is characterized by blunted endothelial nitric oxide (NO) release that contributes to endothelial dysfunction, CVD, and kidney damage.[16] Carotid wall intima–media thickness (CIMT) is used as a surrogate measure of atherosclerosis, which quantitatively measures subclinical coronary atherosclerosis. Increased CIMT of the common carotid artery represents a form of atherosclerosis that is manifested as diffuse arterial wall thickening.[17]

Oxidative stress, inflammation, and endothelial dysfunction are the key triad causing atherosclerosis and subsequent CVD in patients with CKD. Type 2 diabetes mellitus (T2DM) is the most common cause of CKD and an independent risk factor for CVD. Hence, the present study was undertaken to evaluate the markers of oxidative stress, chronic inflammation, endothelial dysfunction, and atherosclerosis in diabetic and nondiabetic CKD pre-dialysis patients.

Materials and Methods

The present cross-sectional, observational study was conducted in the Department of Nephrology, Sri Venkateswara Institute of Medical Sciences, from March 2018 to February 2019, after obtaining institutional ethical clearance. A total of 120 CKD patients not undergoing dialysis treatment were included in the study, after taking written informed consent. The study subjects were divided into two groups: group 1 included 60 CKD pre-dialysis patients with T2DM and group 2 included 60 CKD pre-dialysis patients without T2DM Both group 1 and group 2 were subdivided into two subgroups each based on the glomerular filtration rate (GFR): those with GFR greater or lower than 60 mL/min/m^2.

6 mL of fasting venous blood sample was collected, centrifuged at 3000 rpm for 15 min and the separated serum and plasma were stored at −80°C in deep freezer (Thermo Fischer Scientific, Waltham, MA, USA) until analysis. Urea, creatinine, uric acid, total cholesterol, triglycerides, HDL-cholesterol (HDL-c), calcium, phosphorus, total protein, ALB, and alkaline phosphatase were estimated using commercial kits. LDL and very low-density lipoprotein (VLDL) were calculated using Freidewald's equation.[18] The high-sensitivity C-reactive protein (hsCRP) was estimated by immunoturbidimetry method using commercial kits from Beckman Coulter. All the above parameters were analyzed on clinical chemistry autoanalyzer, Beckman Coulter AU 480 (Beckman Coulter, Brea, CA, USA).

Plasma MDA was measured as thiobarbituric acid reactive substances (TBARS),[19] and FRAP was estimated by the spectrophotometric method of Benzie and Strain[20] using Perkin Elmer lambda 25 UV–Visspectrophotometer (Perkin Elmer, UOB Plaza, Singapore). Plasma IMA was estimated using turbidimetry method on Beckman Coulter AU 480. Serum NO was estimated by Griess method.[21] IL-6 and PON-1 were estimated by enzyme-linked immunosorbent assay (ELISA) technique using the commercial kits from Genxbio Health Sciences Pvt Ltd (Greater Noida, India) with ELISA reader (Transasia Bio-Medicals Ltd, Mumbai, India) and ELISA washer (ERBA Diagnostics, Mannheim, Germany). Measurement of CIMT was done by doing ultrasound examination of the carotids in all study subjects using Voluson 730 Pro Ultrasound machine (GE medical system, Milwaukee, WI, USA) by the same radiologist who was blinded to the clinical information. Measurements were made bilaterally at the carotid bulb, in the distal 1 cm of common carotid artery wall proximal to the bulb and in the proximal-most portion of the internal carotid artery near its origin. The mean of the six readings so obtained was used to calculate the CIMT.

Statistical analysis

All continuous variables were tested for normal distribution with the Kolmogorov–Smirnov test. Normally distributed values were presented as mean ± standard deviation, whereas non-normally distributed values were presented as median (interquartile range). Categorical values were presented as numbers and percentage. Comparisons between two groups were assessed with the Student's unpaired *t*-test or Mann–Whitney test for continuous variables and the χ^2-test for categorical variables, as appropriate. Pearson's rank correlation or Spearman correlation was used to determine correlations of CIMT thickness with other variables. All statistical analyses were performed with Statistical Package for the Social Sciences (SPSS) software (version 16.0; SPSS Inc., Chicago, IL, USA). A *P*-value <0.05 was considered significant.

Results

A total of 120 CKD pre-dialysis patients, divided into group 1 with 60 diabetic patients and group 2 with 60 nondiabetic patients, were included in the study. The mean age of the patients included in group 1 was 58.83 ± 10.7 years and in group 2 was 50.2 ± 17.03 years. The proportion of women was higher than men in both the groups (70% vs. 30% in group 1 and 60% vs. 40% in group 2). The most common etiologies of CKD observed were diabetic nephropathy (48%) and chronic glomerular

nephritis (30%) among the study subjects [Figure 1]. A comparison of the routine laboratory parameters and markers of oxidative stress, inflammation, and endothelial dysfunction between group 1 and group 2 is given in Table 1. A comparison of the markers in early and advanced stages in diabetic and nondiabetic CKD pre-dialysis patients is given in Table 2. The mean serum creatinine, urea and phosphorus levels were higher in group 1 patients than in group 2 patients, (P = 0.924, 0.498 and 0.016, respectively). The median values of serum total protein and triglycerides were lower in group 1 patients than in group 2 patients (P < 0.01 and <0.01). The mean serum ALB, total cholesterol and HDL levels were lower in group 1 patients than in group 2 patients (P < 0.01, <0.01 and <0.01).

The median value of serum IL-6 and hsCRP, were higher in group 1 patients than in group 2 patients (P < 0.001 and 0.283). IL-6 and hsCRP median values were higher in the late stages of CKD compared to the early stages of CKD in both group 1 (P < 0.001 and <0.001) and group 2 patients (P = 0.086 and <0.001). The mean serum MDA and PON-1 levels were higher in group 1 patients than in group 2 patients (P < 0.001 and 0.605). The mean serum MDA and PON-1 levels were higher in late stages than in early stages of CKD in both group 1 (P < 0.004, and <0.012) and in group 2 patients (P < 0.001 and <0.001). The mean serum FRAP, IMA, IMA–ALB ratio and NO levels were lower in group 1 patients than in group 2 patients (P = 0.277, <0.001, 0.06 and 0.026 respectively). In group 1 and group 2 patients, FRAP, IMA, IMA–ALB ratio and NO levels were lower in late stages when compared to early stages of CKD (P = 0.005, 0.064, 0.061 and 0.023) and (P < 0.001, 0.424, 0.582 and <0.001) respectively.

CIMT was increased in group 1 when compared to group 2 (P < 0.001) as shown in Figure 2. In both groups, when compared to early stages, late stages had increased CIMT (P = 0.970 and 0.056)

A correlation analysis of oxidative stress, inflammatory, and endothelial dysfunction markers was done among all 120 study subjects. The results are as shown in Table 3. In all 120 study subjects, endothelial dysfunction marker, CIMT, had a positive correlation with MDA, hsCRP, and IL-6 and a negative correlation with FRAP, PON-1, IMA, IMA–ALB, and NO. This correlation was statistically significant with IL-6 and NO (P = 0.008 and 0.003 respectively)., Table 4 shows the correlation analysis of CIMT with other parameters in group 1 and group 2 patients. CIMT had a significant positive correlation with hsCRP and NO in group 2 patients (P = 0.022 and 0.004).

Discussion

We found that the inflammatory markers, IL-6, and hsCRP were significantly increased in diabetic CKD pre-dialysis patients when compared to nondiabetic CKD pre-dialysis patients in this study. When compared to early stages, late stages had elevated levels of IL-6 and hsCRP in both diabetic and nondiabetic CKD pre-dialysis patients. These findings are suggestive of increased inflammatory state in diabetic and late stages of CKD pre-dialysis patients and are comparable to similar studies.[22,23] The present study showed a statistically significant increase in MDA levels in diabetic group when compared to nondiabetic group, indicating the presence of increased lipid peroxidation in the diabetic group. In both nondiabetic and diabetic CKD patients, the late stages had significantly higher MDA levels when compared to early stages. FRAP and PON-1 levels were decreased in diabetic group when compared to nondiabetic group, indicating increased consumption of antioxidants to compensate for the increased oxidative stress. In both nondiabetic and diabetic CKD pre-dialysis patients, when compared to the early stages, the late stages showed a significant decrease in FRAP and PON-1 levels. In this study, the median levels of IMA were significantly elevated in the diabetic group than in nondiabetic group. In both nondiabetic and diabetic groups, when compared to the early stages, late stages showed a significant increase in

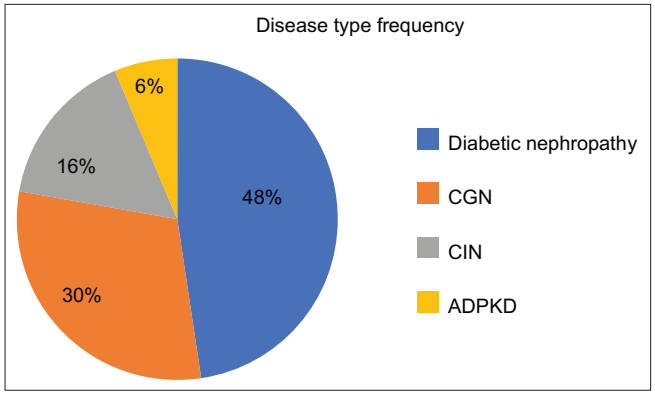

Figure 1: Etiological distribution of 120 patients. CGN = chronic glomerulonephritis, CIN = chronic interstitial nephritis, ADPKD = autosomal dominant polycystic kidney disease

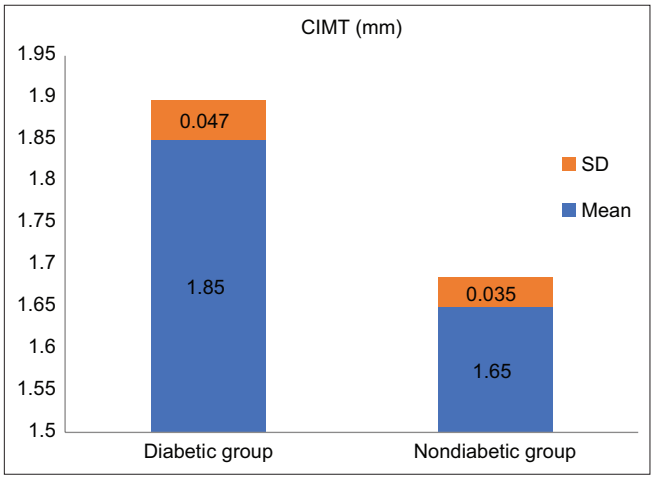

Figure 2: Comparison of CIMT in diabetic and nondiabetic CKD pre-dialysis patients. CIMT = carotid wall intima–media thickness, CKD = chronic kidney disease

Table 1: Comparison of routine laboratory parameters between diabetic (group 1) and nondiabetic (group 2) CKD pre-dialysis patients

Parameter	Group 1	Group 2	*P*
Creatinine (mg/dL)	2.71±1.89	2.68±1.57	0.924
Urea (mg/dL)	59.0±30.33	63.0±34.03	0.498
Calcium (mg/dL)	8.75±0.54	8.96±0.67	0.061
Phosphorous (mg/dL)	5.18±1.34	4.66±0.91	0.016*
Calcium–phosphorus product (mg/dL)	46.68 (27.23–59.34)[a]	44.72 (29.43–53.35)[a]	0.483
Total protein (g/dL)	6.40 (5.9–7.3)[a]	7.5 (6.7–8.0)[a]	<0.01*
Albumin (g/dL)	3.486±0.30	3.94±0.19	<0.01*
Total cholesterol (mg/dL)	146.5±38.3	170.8±28.49	<0.01*
Triglycerides (mg/dL)	118.0 (72–273)[a]	182 (165–270)[a]	<0.01*
HDL-c (mg/dL)	33.57±6.35	44.6±5.50	<0.01*
Malondialdehyde (µmol/L)	3.69±0.19	2.47±0.13	<0.001*
FRAP (mmol/L)	397.63±20.65	430.11±20.27	0.277
PON-1 (ng/mL)	32.56±0.89	31.63±0.99	0.605
IMA (Absorbance Units)	0.310±0.017	0.369±0.013	<0.001*
IMA–ALB ratio	0.0908±0.005	0.0958±0.003	0.06
Nitric oxide (µmol/L)	21.39±0.67	24.43±0.81	0.026*
hsCRP (mg/L)	5.12 (2.77–10.3)[a]	4.21 (2.02–8.48)[a]	0.283
IL-6 (ng/mL)	30.0 (8.48–38.0)[a]	8.79 (7.82–13.22)[a]	<0.001*
CIMT (mm)	1.85±0.047	1.65±0.035	<0.001*

CIMT=carotid intima–media thickness, CKD=chronic kidney disease, FRAP=ferric reducing antioxidant power assay, HDL-c=high-density lipoprotein-cholesterol, hsCRP=high-sensitivity C-reactive protein, IL-6=interleukin-6, IMA=ischemia-modified albumin, IMA–ALB=ischemia-modified albumin and albumin ratio, MDA=malondialdehyde, PON-1=paraoxonase-1, SD=standard deviation. Data represented as Mean±SD. Group 1: diabetic CKD patients; group 2: nondiabetic CKD patients. [a]Data are presented as median (interquartile range). *Significant

Table 2: Comparison of markers studied in early and advanced diabetic (group 1) and nondiabetic (group 2) CKD pre-dialysis patients

Parameter	Group 1			Group 2		
	Early diabetic CKD	Advanced diabetic CKD	*P*	Early nondiabetic CKD	Advanced nondiabetic CKD	*P*
MDA (µmol/L)	3.28±0.19	4.42±0.33	0.004*	2.20±0.15	2.84±0.23	0.012*
FRAP (mmol/L)	441.03±23.81	321.70±32.85	0.005*	528.66±18.01	298.71±18.91	<0.001*
PON-1 (ng/mL)	36.98±0.66	25.93±0.95	<0.001*	36.76±0.69	23.93±0.91	<0.001*
IMA (ABSU)	0.284±0.02	0.357±0.03	0.064	0.360±0.02	0.381±0.02	0.424
IMA–ALB ratio	0.0826±0.005	0.105±0.010	0.061	0.0931±0.005	0.0908±0.006	0.582
Nitric oxide (µmol/L)	22.37±0.55	19.67±1.53	0.023*	25.43±0.84	23.05±1.51	<0.001*
hsCRP (mg/L)	4.92 (0.83–8.17)[a]	6.09 (3.25-17.44)[a]	0.086	2.19 (1.67-4.22)[a]	7.17 (5.27-15.38)[a]	<0.001*
IL-6 (ng/mL)	8.54 (8.14–35.00)[a]	35.0 (30.00-41.00)[a]	<0.001*	7.97 (7.62-8.36)[a]	13.38 (11.24-16.24)[a]	<0.001*
CIMT (mm)	1.86±0.07	1.83±0.05	0.970	1.60±0.05	1.72±0.05	0.056

CIMT=carotid intima–media thickness, CKD=chronic kidney disease, FRAP=ferric reducing antioxidant power assay, hsCRP=high-sensitivity C-reactive protein, IL-6=interleukin-6, IMA=ischemia-modified albumin, IMA–ALB=ischemia-modified albumin and albumin ratio, MDA=malondialdehyde, PON-1=paraoxonase-1, SD=standard deviation. Data represented as Mean±SD. Group 1: diabetic CKD patients; group 2: nondiabetic CKD patients. [a]Data are presented as median (interquartile range). *Significant

IMA levels. This study showed increased oxidative stress in pre-dialysis patients with diabetes and late stages of CKD in both groups which is comparable to similar studies.[24,25] Our study showed statistically significant decrease in HDL levels in the diabetic group when compared to nondiabetic group, suggestive of marked dyslipidemia in the diabetic group. The mean value of NO was significantly decreased in the diabetic group when compared to nondiabetic group. In diabetic and nondiabetic CKD pre-dialysis patients, when compared to early stages, late stages had significantly decreased levels of NO. These findings of our study are comparable to those of similar studies.[16,26] CIMT is both a sensitive and specific marker for atherosclerosis.[27] CIMT was significantly increased in the diabetic group when compared to nondiabetic group in this study. In both diabetic and nondiabetic CKD pre-dialysis patients, when

Table 3: Correlation studies between oxidative stress, inflammatory, and endothelial dysfunction markers of all study subjects

Parameter	CIMT	hsCRP	PON-1	IL-6	IMA	NO
CIMT						
r	1.000	0.182*	−0.77	0.243**	−0.149	−0.278**
P		0.050	0.401	0.008	0.116	0.003
hsCRP						
r	0.182*	1.000	−0.432**	0.433**	0.221	−0.279
P	0.050		0.000	0.000	0.021	0.03
PON-1						
r	−0.077	−0.432**	1.000	−0.675**	−0.162	0.431**
P	0.401	0.000		0.000	0.088	0.000
IL-6						
r	0.243**	0.433**	−0.675**	1.000	−0.036	−0.414**
P	0.008	0.000	0.000		0.709	0.000
IMA						
r	−0.149	0.221*	−0.162	−0.036	1.000	0.099
P	0.116	0.021	0.088	0.709		0.298
NO						
r	−0.278**	−0.279**	0.431**	−0.414**	0.099	1.000
P	0.003	0.003	0.000	0.000	0.298	
MDA						
r	0.125	0.203	−0.346**	0.465**	−0.035	−0.486**
P	0.189	0.034	0.000	0.000	0.712	0.000
FRAP						
r	−0.149	−0.276**	0.573**	−0.480**	−0.060	0.598**
P	0.119	0.004	0.000	0.000	0.533	0.000

CIMT=carotid intima–media thickness, CKD=chronic kidney disease, FRAP=ferric reducing antioxidant power assay, hsCRP=high-sensitivity C-reactive protein, IL-6=interleukin-6, IMA=ischemia-modified albumin, MDA=malondialdehyde, NO=nitric oxide, PON-1=paraoxonase-1, *r*: correlation coefficient. Group 1: diabetic CKD patients; group 2: nondiabetic CKD patients *Significant at the 0.05 level (two tailed); **significant at the 0.001 level (two tailed)

Table 4: Correlation studies between CIMT and other parameters among diabetic (group 1) and nondiabetic (group 2) CKD pre-dialysis patients

Parameter	Group 1			Group 2		
	Parameter	Correlation coefficient (*r*)	*P*	Parameter	Correlation coefficient (*r*)	*P*
CIMT	MDA	−0.051	0.710	MDA	0.019	0.889
CIMT	FRAP	0.045	0.743	FRAP	−0.241	0.074
CIMT	hsCRP	0.012	0.927	hsCRP	0.299	0.022*
CIMT	IL-6	0.042	0.750	IL-6	0.235	0.070
CIMT	PON-1	0.048	0.718	PON-1	−0.193	0.139
CIMT	IMA	−0.182	0.184	IMA	0.088	0.517
CIMT	IMA–ALB	−0.189	0.167	IMA–ALB	0.025	0.853
CIMT	NO	0.035	0.801	NO	−0.373	0.004*

CIMT=carotid intima–media thickness, CKD=chronic kidney disease, FRAP=ferric reducing antioxidant power assay, hsCRP=high-sensitivity C-reactive protein, IL-6=interleukin-6, IMA=ischemia-modified albumin, IMA–ALB=ischemia-modified albumin and albumin ratio, MDA=malondialdehyde, NO=nitric oxide, PON-1=paraoxonase-1. Group 1: diabetic CKD patients; group 2: nondiabetic CKD patients. *Significant

compared to early stages, late stages had increased thickness. Our study showed significant increase in endothelial dysfunction in pre-dialysis patients with diabetes and late stages of CKD with similar findings in other study.[27]

Our study showed statistically significant correlation between oxidative stress and inflammatory markers among all study subjects. Endothelial dysfunction marker, CIMT, showed correlation with oxidative stress and inflammatory markers among all study subjects, with a statistically

significant correlation with hsCRP, IL-6, and NO. In both diabetic and nondiabetic groups, CIMT showed correlation with oxidative stress and inflammatory markers, suggesting their pathological role in atherosclerosis.

Conclusions

The findings of our study showed significantly increased inflammation, oxidative stress, endothelial dysfunction, and atherosclerosis in diabetic CKD pre-dialysis patients when compared to nondiabetic CKD pre-dialysis patients. Late stages of CKD showed significantly increased inflammation, oxidative stress, endothelial dysfunction, and atherosclerosis when compared to early stages in both diabetic and nondiabetic CKD pre-dialysis patients. These findings are suggestive of increased risk of mortality and morbidity due to CVD in diabetic and late or advanced stages of CKD pre-dialysis patients.

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Conflicts of interest

There are no conflicts of interest.

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