

Renal Function Evaluation in Secondary Amyloidosis According to Location of Deposition

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Abstract: It aimed to evaluate the renal functions according to the accumulation site of amyloid in patients diagnosed with secondary amyloidosis by renal biopsy. Fifty patients diagnosed with secondary amyloidosis, who referred to the nephrotic syndrome outpatient clinic included in the study. According to the findings of renal biopsy, only-glomerular amyloid deposition (group- 1) detected in 9 patients and glomerular+ tubulointerstitial deposition (group- 2) identified in 41 patients. Serum creatinine, creatinine clearance, and total proteinuria levels compared between groups at the time of presentation and on 3rd, 6th, 12th, and 24th months. Initial and subsequent serum creatinine, creatinine clearance, and total proteinuria levels not found to be significantly different between groups ($p>0,05$ for all). Among subjects with only-glomerular deposition, statistically significant descents in total proteinuria, when compared to initial levels, were observed from the beginning of the 6th month to the end of the 24th month ($p<0,05$). On the other hand, subjects with both glomerular + tubulointerstitial deposition, statistically significant descents in total proteinuria levels observed from the beginning of follow-up to the end of the 24th month ($p<0,01$). In subjects with both glomerular + tubulointerstitial accumulation, a statistically significant increase in serum creatinine, compared to baseline levels, observed in 12th and 24th months ($p<0,01$). According to the biopsy findings, progressive deterioration of renal functions and an increase in proteinuria were higher in patients with both glomerular and tubulointerstitial amyloid deposition than patients with only-glomerular removal.

Keywords: renal biopsy; deposition; secondary amyloidosis

INTRODUCTION

Amyloidosis is a disease caused by the extracellular accumulation of a fibrillary protein called amyloid in various organs (Westermarck et al., 2005). Amyloid fibrils may be stored locally and involve almost all organ systems depending on the biochemical structure of the amyloid precursor proteins. Amyloid fibril deposition may not lead to any significant clinical manifestations, but on the other hand, it may accompany severe pathophysiological changes, as well. The disease usually progresses between these two extremes (Husby et al., 1994). Despite technological advances, no clinical, serological, or radiological data have fully substituted renal biopsy for the identification of amyloidosis (Pepys et al., 2001 and Kebbel et al., 2006 and Bergesio et al., 2007 and Lachmann et al., 2004). After the diagnosis of amyloidosis, the determination of amyloid type is essential in terms of treatment and

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prognosis of the disease (Picken et al., 2007). Secondary (reactive, modified, or AA) amyloidosis most commonly occurs during chronic inflammatory diseases, infections, and neoplastic diseases. Familial Mediterranean fever (FMF), chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, Behçet's disease, Crohn's disease, and ulcerative colitis are among the most common chronic inflammatory diseases. At the same time, tuberculosis, osteomyelitis, and bronchiectasis are the frequent infectious and thyroid medullary cancer, Hodgkin lymphoma and insulinoma are the numerous neoplastic causes (Cohen et al., 1991 and Seldin et al., 2005 and Falk et al., 1997 and Elżbieta et al., 2019). Renal involvement in systemic amyloidosis is a common complication and indicates a poor prognosis. Patients present with clinical manifestations ranging from proteinuria to nephrotic syndrome, and renal biopsy is required in a significant proportion of patients to serve as a diagnostic and also a prognostic tool. Therefore, the clinical correlation with the storage type, severity, prevalence and clinical reflection of the kidney biopsy will enable the prognosis of the disease to be predicted (Lachmann et al., 2004 and Falk et al., 1997 and Elżbieta et al., 2019 and Lachmann et al., 2007 and Gertz et al., 1991).

The distribution pattern of glomerular amyloid deposits, glomerular inflammatory reaction, and tubular atrophy in the renal biopsy are independent risk factors for proteinuria level and renal damage (Verine et al., 2007). Renal failure usually refers to severe glomerular amyloidosis and tubular atrophy. In contrast, renal prognosis in patients with renal amyloidosis does not always have a morphological explanation (Dikman et al., 1981). To understand how this clinical difference occurs, we wanted to clarify the results of amyloid deposition, especially in the glomerular and tubulointerstitial space. This study aimed to evaluate the renal biopsy findings for the amyloid storage location and according to renal functions of patients with secondary amyloidosis.

MATERIALS – METHODS

Patient population and follow-up

Fifty patients admitted to the nephrotic syndrome outpatient clinic of İstanbul Göztepe Training and Research Hospital from 1994 to 2010 and diagnosed with secondary amyloidosis after undergoing renal biopsy included in the study. The ethics committee approved the review of İstanbul Göztepe Training and Research Hospital. Age, sex, serum urea, creatinine, 24-hour urine total protein (glomerular filtration rate, clinical signs at presentation (such as edema, hematuria, proteinuria, oligoanurated hypertension) and an indication of renal biopsy (nephrotic syndrome, nephritic syndrome and asymptomatic urine findings, etc.) were collected retrospectively. Serum urea, creatinine, and 24-hour urine total protein performed by photometric measurement methods (Architect C16000 clinical biochemistry analyzer, Abbott®, USA). In calculating the glomerular filtration rate, the formula proposed by the Study Group's Modification of Diet in Renal Disease (MDRD) was used (Levey et al., 1999). The relevant medical history like underlying chronic diseases (FMF, COPD, rheumatoid arthritis, Behçet's disease, ankylosing spondylitis, bronchiectasis, and tuberculosis, etc.) and currently used antiproteinuric drugs (angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) provided.

Renal biopsy report of each case obtained and findings of glomerular involvement, tubular involvement, tubular atrophy, and interstitial fibrosis recorded. Based on renal biopsy, amyloid involvement dichotomized into two groups according

to whether the involved compartment was only-glomeruli (Group-1) or both glomeruli and tubulointerstitium (Group-2). Stage 1, in the scoring system of renal amyloidosis, corresponds to Group-1 in our study, whereas stage 2 and 3 match with group-2 (Sen et al., 2010).

The follow-up time started from the month of renal biopsy (baseline) and continued with data collection on 3rd, 6th, 12th, and 24th months. The final status of the patients, including active disease, remission (complete and partial), and relapse, was considered to evaluate prognosis and treatment outcome (Table-1).

Table-1: Active, remission and relapse criteria of the disease

Active proteinuria	Proteinuria over 3.5 g/day on 3 consecutive days
Complete remission	Less than 0.2 g/day of proteinuria for 3 consecutive days
Partial remission	Proteinuria between 0.2-3.5 g/day for 3 consecutive days
Proteinuria relapse	In patients at complete remission, proteinuria over 0.2 g/day for at least one week
Nephrotic syndrome relapse	Proteinuria more significant than 3.5 g/day for at least one week in patients at complete or partial remission

Pathology

The following morphological findings used in Group-1 and Group-2 classification:

1-Amyloid involvement of the glomerular compartment (total number of glomeruli, number of globally sclerotic glomeruli, glomerular participation type, a diameter of glomeruli, degree of glomerular amyloid, accumulation of glomerular nodular amyloid (segmental/global presence)

2-Amyloid involvement of the tubular-interstitial compartment (vasa recta involvement, tubular atrophy/fibrosis, appearance, quality and severity of interstitial inflammation, accumulation and diameter of interstitial amyloid, amyloid deposition in the tubular basement membrane damage)

Statistical analysis

NCSS (Number Cruncher Statistical System) 2007 & PASS 2008 Statistical Software (Utah, USA) program used for statistical analysis. The normality of distribution examined by using the Kolmogorov-Smirnov test. Along with descriptive statistical methods (mean, standard deviation), for comparison of quantitative and normally distributed data. Although normal distribution was determined, non-parametric tests used due to the relatively small sample size. Mann-Whitney U t-test used for between-group differences. Wilcoxon Signed Ranks test used for within-group differences. The chi-square test used to evaluate the qualitative data. Significance was assessed at $p < 0.05$.

RESULTS AND DISCUSSION

Baseline characteristics and morphological findings

The mean age at the time of diagnosis was 46.92(13.3) years (M: F=1.27: 1). The most common cause of secondary amyloidosis was FMF, followed by COPD and rheumatoid arthritis (Table-2). While only glomerular involvement detected in 9 of 50 cases (Group-1), 41 of them had both glomerular and tubulointerstitial relationships (Group-2). Glomerulosclerosis was observed in 17 of the cases, while mesangial proliferation and inflammatory cells in the glomeruli observed in the remaining 33 cases. Tubular atrophy (82%) was common and mostly mild (76%).

Inflammatory reaction was present in 32% of the cases; inflammatory cells were generally of the mixed (mononuclear + polymorphonuclear) type.

Table 2: Diseases causing AA (Secondary) amyloidosis

Underlying Chronic Disease	Biopsy Finding		
	Group-1 n:9 (%)	Group-2 n:41 (%)	Total n:50 (%)
FMF	8 (88,9%)	20 (48,8%)	28 (56,0%)
COPD	0 (0%)	8 (19,5%)	8 (16,0%)
Romatoid artritis	1 (11,1%)	5 (12,2%)	6 (12,0%)
Ankylosing spondylitis	0 (0%)	2 (4,9%)	2 (4,0%)
Gout	0 (0%)	2 (4,9%)	2 (4,0%)
Chronic pyelonephritis	0 (0%)	2 (4,9%)	2 (4,0%)
Tuberculosis	0 (0%)	2 (4,9%)	2 (4,0%)
Behcet 's disease	0 (0%)	1 (2,4%)	1 (2,0%)
Hodgkin Lymphoma	0 (0%)	1 (2,4%)	1 (2,0%)
Ulcerative colitis	0 (0%)	1 (2,4%)	1 (2,0%)

FMF; familial mediterranean fever

COPD; Chronic obstructive pulmonary diseases

Clinicopathological correlation

Total proteinuria

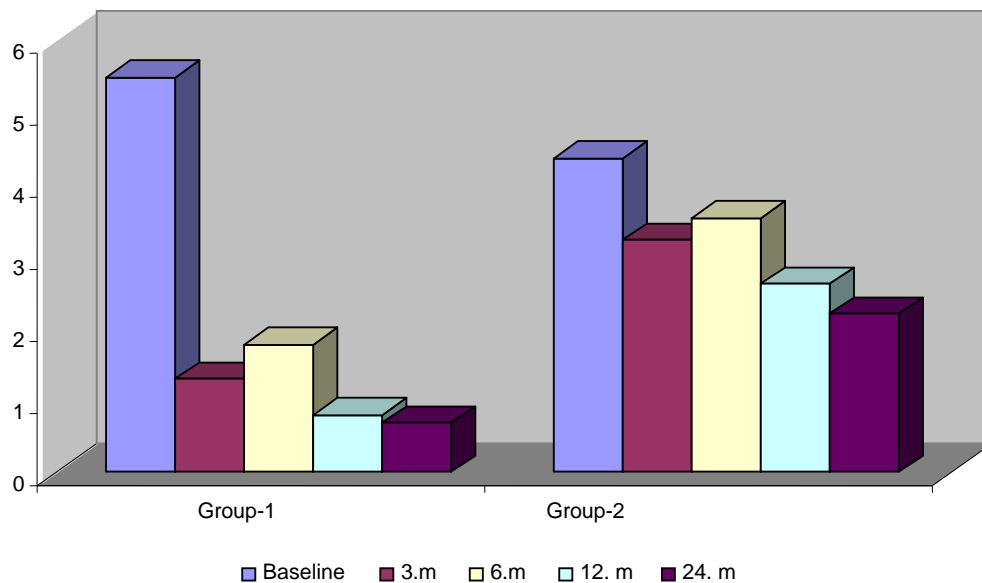
There was no statistically significant change in total proteinuria in the 3rd month, compared to baseline, in Group-1 patients ($p > 0.05$). However, when the absolute proteinuria values examined from the beginning of the 6th month to the end of the 24th month, statistically significant decreases compared to baseline were observed ($p < 0.05$). About group-2, statistically, significant descents in total proteinuria levels were seen from the beginning of follow-up to the end of the 24th month ($p < 0.01$). There was no significant difference between the groups ($p > 0.05$) (Table-3, Figure-1).

Table 3: Evaluation of Total Proteinuria (mg / 24 h) based on Biopsy Finding

Total Proteinuria (mg/24 h)	Biopsy Finding		
	Group-1 Mean±SD	Group-2 Mean±SD	p^*
Baseline	5,11±5,17	4,71±3,46	0,785
3rd month	2,45±2,54	3,78±2,84	0,160
6th month	1,88±1,77	3,92±3,54	0,119
12 th month	1,78±2,07	3,35±3,21	0,091
24 th month	1,41±1,69	2,94±2,76	0,082
Baseline-3rd month	0,086	0,031	
Baseline-6th month	0,028*	0,048	
Baseline-12th month	0,028*	0,048	
Baseline-24th month	0,018*	0,002	

*Mann-Whitney U t-test was used for between-group differences. Wilcoxon Signed Rank test was used for within-group differences.

Figure-1: Total proteinuria (gr / 24 h) levels by months



Serum creatinine levels

There was no statistically significant change in creatinine levels in Group-1 patients at the 3rd, 6th, 12th, and 24th months compared to baseline ($p > 0.05$). Regarding the change in creatinine levels in group-2 patients, there was no significant difference ($p > 0.05$) between baseline and 3rd and 6th months. On the contrary, in the 12th and 24th months, a statistically significant rise in creatinine was seen compared to baseline levels ($p < 0.01$).

Glomerular filtration rate

Twelve percent of all cases had an end-stage renal failure at the time of renal biopsy. In Group-1, there was no statistically significant change in MDRD GFR between the baseline and the 3rd, 6th, 12th, and 24th months' rates ($p > 0.05$). However, MDRD GFR significantly decreased in Group-2 cases at 12th and 24th months compared to baseline ($p > 0.05$) (Table -4 and Figure-2)

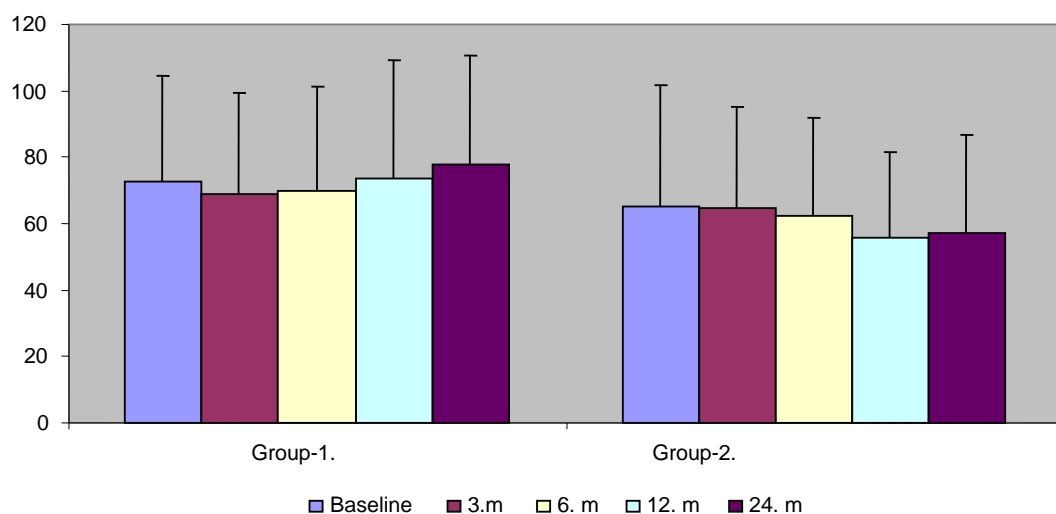
Figure-2: MDRD GFR (mL / min / 1.73 m²) changes by months

Table 4: Evaluation of MDRD GFR (mL / min / 1.73 m2)

MDRD GFR	Biopsy Finding		<i>p</i> *
	Group-1 Mean±SD	Group-2 Mean±SD	
Baseline	72,67±32,05	65,34±30,61	0,522
3rd month	68,89±36,61	64,90±30,05	0,730
6th month	69,78±31,24	62,53±29,47	0,512
12th month	73,67±35,47	55,85±25,81	0,087
24th month	71,87±32,74	57,25±29,57	0,084
Baseline-3rd month	0,268	0,815	
Baseline-6th month	0,531	0,102	
Baseline-12th month	0,740	0,001	
Baseline-24th month	0,953	0,009	

MDRD GFR; Modification of Diet in Renal Disease glomerular filtration rate.

*Mann-Whitney U t-test was used for between-group differences.

Wilcoxon Signed Rank test was used for within-group differences

Drugs used

Use of ACEi, ARB and the combination of ACEi and ARB as anti-proteinuric treatment were compared between groups and not found to be statistically significant (Table-5).

Table 5: Use of ACEi, ARB and ACEi + ARB combination

		Biopsy Finding		<i>P</i> *
		Group-1 n (%)	Group-2 n (%)	
Baseline treatment	ACE	4 (50%)	26 (66,7%)	0,575
	ARB	1 (12,5%)	5 (12,8%)	
	ACE+ARB	3 (37,5%)	8 (20,5%)	
3rd month treatment	ACE	3 (33,3%)	23 (57,5%)	0,265
	ARB	1 (11,1%)	6 (15%)	
	ACE+ARB	5 (55,6%)	11 (27,5%)	
6th month treatment	ACE	3 (33,3%)	22 (56,4%)	0,362
	ARB	1 (11,1%)	5 (12,8%)	
	ACE+ARB	5 (55,6%)	12 (30,8%)	
12th month treatment	ACE	2 (22,2%)	17 (43,6%)	0,457
	ARB	2 (22,2%)	8 (20,5%)	
	ACE+ARB	5 (55,6%)	14 (35,9%)	
24th month treatment	ACE	3 (37,5%)	17 (47,2%)	0,449
	ARB	1 (12,5%)	9 (25%)	
	ACE+ARB	4 (50%)	10 (27,8%)	

ACEi; angiotensin converting enzyme inhibitors,

ARB; angiotensin receptor blockers.

*Chi- square test was used for between-group differences

Evaluation of the final status

During the renal biopsy, 46% of the patients were in remission (complete and partial), and 54% were in active proteinuria phase. At the end of the 12th month, 28% of patients had progressive proteinuria, 58% had a remission, 2% had proteinuria relapse, and 12% had nephrotic syndrome relapse. At the end of 24 months, the remission rate increased to 70% (12% complete and 59% partial), while the actual proteinuria rate decreased to 18%.

Among patients with only-glomerular involvement, 55.6% had progressive proteinuria at the time of biopsy. At the end of 24 months, all but one patient had complete or partial remission. In patients with both glomerular and tubulointerstitial involvement, 53.7% had progressive proteinuria at baseline while this rate was 36.6% at the end of the 3rd month, 31.7% at the end of the 6th month, and 23.1 % at the end of the 24th month. Finally, at the end of the 24th month, 69.2% of the patients were in remission (Table-6).

Table 6: Final Assessment of Proteinuria Levels

Final status		Biopsy Finding	
		Group-1 n (%)	Group-2 n (%)
Baseline	Active proteinuria	5 (%55,6)	22(%53,7)
	Complete remission	0	1 (%2,4)
	Partial remission	4 (%44,4)	18 (%43,9)
3rd month	Active proteinuria	2 (%22,2)	15 (%36,6)
	Complete remission	2 (%22,2)	1 (%2,4)
	Partial remission	5 (%55,6)	19 (%46,3)
	Proteinuria relapse	0	1 (%2,4)
	NS relapse	0	5 (%12,2)
6th month	Active proteinuria	1 (%11,1)	13 (%31,7)
	Complete remission	2 (%22,2)	4 (%9,8)
	Partial remission	5 (%55,6)	19 (%46,3)
	NS relapse	1 (51,1)	5 (%12,2)
	Active proteinuria	1 (%11,1)	13 (%31,7)
12th month	Complete remission	1 (%11,1)	4 (%9,8)
	Partial remission	5 (%55,6)	19 (%46,3)
	Proteinuria relapse	1 (%11,1)	0
	NS relapse	1 (%11,1)	5 (%12,2)
	Active proteinuria	0	9 (%23,1)
24th month	Complete remission	3 (%33,3)	4 (% 9.7)
	Partial remission	5 (%55,6)	25 (% 60.9)
	Proteinuria relapse	0	1 (%2,6)
	NS relapse	1 (%11,1)	2 (%5,1)

NS; Nephrotic syndrome

In this study involving patients diagnosed with secondary amyloidosis, kidney functions were evaluated according to the renal amyloid storage location, whether in only-glomerular or both glomerular+tubulointerstitial compartment, in 24 months. In the end, no significant difference found about serum creatinine, MDRD creatinine

clearance, and total proteinuria levels between the predefined groups. However, within each group, throughout 24 months, in comparison to the baseline month, the renal loss was found to be higher in glomeruli + tubulointerstitium-involved patients compared to only-glomeruli-involved patients. It is also noteworthy to state that a considerable proportion of the patients (56%) with secondary amyloidosis had to coexist FMF in the present study emphasizing the relatively high frequency of this disease in Turkey.

The number of studies in the literature on the amount and localization of amyloid stored in the kidney is limited (Shiiki et al., 1988 and Watanabe et al., 1975 and Falck et al., 1983; and Westermarck et al., 1979). Existing studies on morphological findings predicting proteinuria levels in secondary amyloidosis have been established linear correlation with the severity of glomerular amyloid deposition (Verine et al., 2007 and Kaplan et al., 1999). Proteinuria severity correlates with the presence of podocyte destruction rather than the amount of amyloid in the glomeruli (Dikman et al., 1981). In our study, although glomerular and tubulointerstitial involvement not evaluated separately, there was a numerical difference between the groups in terms of total proteinuria decrease. Although this situation was not statistically significant, the decline compared to baseline was approximately 3.5 times for group 1 and less than half for group 2. In a study, closely resembling our sample size and primary etiology, the results of renal function change and proteinuria reduction found to be similar. (Abdallah et al., 2013). While evaluating these changes in proteinuria levels, intensive use of ACEi, ARB, or ACEi, together with ARB, should not be ignored in both study groups. In a study where ACEi (ramipril) and ARB (telmisartan) were used together as a dual effect, or only ACEi or ARB used as monotherapy, a significantly higher incidence of hyperkalemia observed in the double blockage arm. (Heerspink et al., 2014). Currently, the combination of ACEi and ARB is no longer in use because of the considerable risk of hyperkalemia. Since the study covers the years 1994-2010, the combination therapy had used in Turkey at that time.

Dikman et al. reported a rapid loss of renal function in patients with renal amyloidosis with tubular atrophy (Dikman et al., 1981). Verine et al. also regarded the tubular atrophy and the prevalence and type of amyloid deposition as independent variables for renal function (Verine et al., 2007). Supporting these trials, in the present study, glomerular amyloid deposition coupled with tubulointerstitial involvement, which defined as group-2, exhibited a prominent renal loss, particularly after 1st year in the follow-up. However, in the study arm with only-glomerular responsibility, the renal reserve was better preserved.

Results from analysis, including 97 patients with primary and secondary amyloidosis, ended up with a five and 10-year survival rate of 30% and 20%, respectively. The authors concluded that the strongest prognostic determinants of renal survival are amyloid-induced renal damage and serum creatinine level at the time of biopsy. Furthermore, AA amyloidosis found to be far more associated with tubulointerstitial loss as compared to AL amyloidosis (Sasatomi et al., 2001). However, Dikman et al. argued that there is not always a morphological explanation for the frequently irreversible decrease in renal function (Dikman et al., 1981). This may be a result of the rate of development of amyloidosis, they added. Because the risk and price of development of amyloidosis vary according to genotypes (Nakamura et al., 2006), nevertheless, a recent article uncovered the conclusion that renal damage not expected to be associated with amyloid deposition (Kuroda et al., 2017 and Kuroda et al., 2019).

Selection bias resulting from retrospective work is our main limitation. The other limitation is the small number of patients included. The third one is the lack of standardization in the antiproteinuric treatment agents among patients and last relates to the absence of rebiopsies during the follow-up, to determine whether a non-glomerular involvement occurs in group-1.

CONCLUSION

According to the biopsy findings, progressive deterioration of renal functions and an increase in proteinuria were higher in patients with both glomerular and tubulointerstitial amyloid deposition than patients with only-glomerular removal. Therefore the pathology report in patients with renal amyloidosis should incorporate detailed morphological findings aiding better prognostication (the type of glomerular amyloid accumulation and renal damage score = degree of glomerular accumulation + tubulointerstitial accumulation) rather than be used as a general diagnostic assay.

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CONFLICT OF INTEREST

The authors have declared that they have no significant relationships with or financial interests in any commercial company.

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