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Bone Mineral Density and Biochemical Markers of Bone Turnover During the First Year of Injury in Patients with Spinal Cord Injury
研究脊髓創傷患者在第一年的骨質密度和骨代謝生化指標

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ABSTRACT

Background: Spinal cord injury (SCI) is associated with bone mass loss that can be complicated by fractures, which result in further disabilities for patients. After a SCI, the body starts losing large amounts of calcium and other minerals in the urine (demineralisation). This study aimed to assess the changes in bone mineral density (BMD) during the 1st year of acute SCI in patients with neurological deficit.
Methods: A total of 95 patients with acute SCI and neurological deficit were evaluated in this prospective study. Haematological investigations such as evaluation of serum calcium, serum phosphate, serum creatinine, and serum alkaline phosphatase (ALP) were carried out. Urinary investigations such as 24-hour urinary creatinine level and excretion of calcium and phosphate in the urine were measured. BMD was measured using dual-energy X-ray absorptiometry scan with Hologic QDR 2000 scanner (Explorer). All of the aforementioned parameters were measured again at 3, 6, and 12 months.
Results: Serum ALP at 1-year follow up was significantly raised ($p < 0.05$). The BMD at 1-year follow up had statistically significant lower values than the initial BMD at the hip ($p < 0.05$), proximal tibia ($p < 0.001$), and distal tibial epiphysis ($p < 0.001$). The BMD in motor-complete SCI patients [American Spinal Injury Association (ASIA) grades A and B] had significant lower values than motor-incomplete SCI patients (ASIA C and D) at the hip ($p < 0.05$) and proximal tibial epiphysis ($p < 0.05$).
Conclusion: There was a marked decrease in BMD in metaphyseal sites than below the neurological deficit level with maximum decrease at the proximal tibia during the 1st year of SCI. Although the markers of osteoblastic activity did not show much change, the decrease in BMD was influenced by the neurological recovery after SCI.

中 文 摘 要

背景: 脊髓創傷（SCI）引發骨質流失可併發骨折，使患者進一步喪失功能。脊髓創傷後，身體開始在尿液中丟失大量的鈣和其他礦物質（去礦物質化）。本研究旨在評估在第一年急性脊髓創傷伴隨神經功能缺損的骨質密度（BMD）之變化。
方法: 在這前瞻性的研究中，評估了95個患有急性脊髓創傷伴隨神經功能障礙的病例。包括檢驗他們血清中的鈣、磷、肌酐和鹼性磷酸酵並測量24小時尿中排泄的肌酐、鈣和磷。使用Hologic公司的QDR 2000雙能X射線光子吸收測定（DEXA）掃描儀（探索者）測量BMD。並於第三、六和十二個月隨訪復查量度上述之所有參數。
結果: 在一年的隨訪復查，血清鹼性磷酸酶顯著上升（$p < 0.05$），骨質密度比較起初的數值在髖關節（$p < 0.05$），脛骨近端（$p < 0.001$）和脛骨遠端骨骺（$p < 0.001$）處明顯較低。完全失去活動功能的SCI患者（美國脊髓創傷協會 ASIA: A级與B级）之BMD比較那些非完全失去活動功能的（ASIA: C级與D级），在髖關節（$p < 0.05$）和近端脛骨骨骺（$p < 0.05$）處的量度數值明顯較低。
結論: 脊髓創傷後的第一年，在脊髓損傷以下的幹骺端，骨質密度（BMD）顯著下降，其在脛骨近端的減少為最多。雖然成骨細胞的活性指標沒有出現太大的變化，但神經功能的恢復卻影響BMD的數值。

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Introduction

Spinal cord injury (SCI) is associated with bone mass loss that can be complicated by fractures, which result in further disabilities for patients.[1] After an SCI, the body starts losing large amounts of calcium and other minerals in the urine (demineralisation). This rapid loss of bone minerals continues for 6–16 months after the injury, following which it levels off to nearly half the amount. Bone loss occurs primarily below the level of neurological deficits. Although unloading is an important factor in the pathogenesis of bone loss in SCI patients, neuronal lesion and hormonal changes also seem to be involved in this process.[2]

From a research perspective, dual-energy X-ray absorptiometry (DEXA), peripheral quantitative computed tomography, magnetic resonance imaging, and quantitative ultrasound have been used to characterise skeletal changes after SCI. DEXA is currently the most commonly used tool to assess bone mineral density (BMD). Most studies in literature that assessed BMD in SCI patients were retrospective cross-sectional studies and compared the patients with controls. The longitudinal studies available included a small number of patients.[3–5] This study aimed at assessing the changes in BMD in the 1st year of acute SCI in patients with neurological deficit ($n = 95$).

Materials and methods

One-hundred-and-six patients (79 males and 27 females) sustained acute SCI with neurological deficit and were admitted in our tertiary level health-care institute between 2007 and 2009. Only patients with Grade A or B of the American Spinal Injury Association (ASIA) impairment scale[6] with impaired motor control below the injury level at the initial state were enrolled for this study. None of the patients had metabolic diseases or other conditions known to influence their calcium metabolism or BMD, and none of the participants had received treatment influencing these parameters such as intake of steroids, oestrogens, bisphosphonates or fluorides, thyroid hormones, lithium, antiepileptics, or antiandrogens. All our female patients were premenopausal. Eleven patients died before completion of the minimum 1-year follow up due to multiple causes such as respiratory tract infection, cardiac arrhythmias, and pleural effusions. Thus, only 95 patients were included in the study.

The patients were given detailed information about the purpose of the study and written consent was obtained from all the participants. A complete medical history of the patients was recorded followed by thorough physical examination and neurological documentation. Haematological investigations including serum calcium, serum phosphate, serum creatinine, and serum alkaline phosphatase (ALP) were carried out. The 24-hour urinary creatinine level and calcium and phosphate excretion in the urine were measured. The BMD was measured by a DEXA scan with a Hologic QDR 2000 scanner (Explorer). All of the aforementioned parameters were repeated at 3, 6, and 12 months after the SCI. A single operator performed all the scans in this study. The patients showing no signs of motor neurological recovery were considered as motor complete (ASIA A and B; 41 patients) and patients showing signs of motor neurological recovery were considered as motor incomplete (ASIA C and D; 54 patients). At the end of the study, statistical analysis was conducted. Unpaired t tests were performed to determine group differences, whereas paired Student t tests were used to determine significant differences within the pairs. For all tests, $p < 0.05$ was considered significant. The relationships between various parameters were calculated using Pearson correlation (r) analysis and regression analysis. Ethical approval was obtained from the Institutional Review Board and consent was obtained from all the patients.

Results

Table 1 shows the sociodemographic profile of the population. Table 2 shows the comparison of various biochemical parameters in serum and urine during the study period. Although the serum phosphate level was increased at the 3-month, 6-month, and 1-year follow up, it was not statistically significant. Serum ALP at 1-year follow up was significantly increased ($p < 0.05$) in comparison with the values at the time of presentation. Other biochemical parameters did not reveal statistically significant differences.

Table 3 showed decreasing trends of BMD in all patients at the hip, proximal tibial, and distal tibial epiphyses with increasing duration of injury. After excluding the lumbar spine BMD of operated patients because of the pedicle screws, we found that the initial values of BMD and values at 1-year follow up showed statistically significant difference at the hip ($p < 0.05$), proximal tibia ($p < 0.001$), and distal tibial epiphysis ($p < 0.001$). Figure 1 shows the decreasing trends of BMD in the tetraplegic group and the paraplegic group at the hip, proximal tibial, and distal tibial epiphyses with increasing duration of injury. The decreasing trend of BMD in all measured areas below the neurological injury level was seen in tetraplegic patients (Figure 1) including the distal end of radius ($p < 0.05$). The BMD of the distal end of radius was 25% less at 1 year when compared with the initial values.

There were also decreasing trends in BMD of paraplegic patients at the hip, proximal tibia, and distal tibia (Figure 1). We noted a decrease of 14.4% in BMD at the hip, 23% at the proximal tibia, and 21.6% at the distal tibial epiphysis at 1 year in operated patients ($n = 21$ patients). There was an 18.7% decrease in BMD at the hip, 21.5% decrease at the proximal tibia, and 19.3% decrease at the distal tibial epiphysis in nonoperated patients ($n = 74$ patients; Figure 2). They were statistically significant when compared with the initial values (Figure 2). However, there was no significant decrease of BMD at the lumbar spine showing dissociated hip–spine demineralisation.

Table 1
Sociodemographic characteristics of the study population ($N = 95$)

Characteristics	Number	Percentage
Sex		
Male	71	74.7%
Female	24	25.3%
Age	33.3 y (average) (range: 19–60 y)	
Paraplegics	75	78.9%
Tetraplegics	20	21.1%
Level of injury		
Cervical	20	21%
Dorsal	27	28.4%
Dorso-lumbar junction injuries (D10–L2)	35	36.9%
Lumbar	13	13.7%
Neurological status at the time of admission (ASIA impairment scale)		
A	53	55.8%
B	42	44.2%
C	NIL	0%
D	NIL	0%
E	NIL	0%
Neurological status at 1 y after injury (ASIA impairment scale)		
A	22	23.15%
B	19	20%
C	39	41.05%
D	15	15.8%
E	NIL	0%
Management		
Conservative	74	77.89%
Operative	21	22.1%

ASIA = American Spinal Injury Association.

Table 2
Comparison of various biochemical parameters in the serum and urine during the study period

	Initial	3 mo	6 mo	12 mo
Haemoglobin (g%)	11.6 ± 1.7	11.0 ± 1.2	11.1 ± 1.4	10.2 ± 1.6
Serum calcium (mg%)	8.8 ± 1.2	8.7 ± 1.4	8.6 ± 2.1	8.3 ± 0.8
Serum phosphate (mg%)	3.8 ± 1.2	4.0 ± 1.4	4.1 ± 0.4	4.2 ± 0.8
Serum creatinine (mg%)	0.7 ± 0.16	0.8 ± 0.18	0.7 ± 0.2	0.80 ± 0.23
Serum alkaline phosphatase (IU)	195.2 ± 47.1	214.2 ± 28.3	227.9 ± 30.2	231.3 ± 30.5*
Total serum protein (mg%)	6.24 ± 0.6	6.4 ± 0.8	6.5 ± 2.1	6.4 ± 1.0
24-h urine calcium (mg/day)	109.5 ± 24.5	115.4 ± 30.2	116.2 ± 26.2	120.7 ± 39.0
24-h urine phosphate (g/day)	1.06 ± 0.16	1.29 ± 0.21	1.06 ± 0.12	1.08 ± 0.03
24-h urine creatinine (g/day)	0.9 ± 0.34	0.7 ± 0.24	0.8 ± 0.26	0.84 ± 0.30

IU = International Unit.
* Statistically significant difference between the initial and 1-year follow-up values.

Table 3
BMD values in all patients at 3-, 6-, and 12-month follow-ups

	Initial	3 mo	6 mo	12 mo
Lumbar spine	0.956	1.17	1.18	1.21
Hip	0.968	0.925	0.9	0.77*
Proximal tibia	1.02	0.969	0.908	0.74*
Tibial diaphysis	1.11	1.04	1.04	1.005
Distal tibial epiphysis	0.985	0.93	0.901	0.75*
Distal radius	0.61	0.599	0.59	0.57

BMD = bone mineral density.
* Statistical difference between the initial and 12-month values.

In motor-complete SCI patients (ASIA A and B; $n = 41$ patients), there was a 21.6% decrease of BMD at the hip, 30.8% at the proximal tibia, and 19.5% at the distal tibial epiphysis, all of which were statistically significant (Figure 3). However, the decrease in BMD at the tibial diaphysis and distal radius in motor-complete SCI patients was not statistically significant. In motor-incomplete SCI patients (ASIA C and D; $n = 54$ patients), there was a 10.3% decrease of BMD at the hip, 10.2% at the proximal tibia, and 15.5% at the distal tibial epiphysis at 1 year, all of which were statistically significant (Figure 3). However, the decrease in BMD at the tibial diaphysis and distal radius in motor-incomplete SCI patients was not statistically significant.

In this study, there was no correlation between the BMD of lower extremity and the serum ALP in SCI patients ($r = 0.217$; $p = 0.076$). We found no correlation between total-body BMD and serum calcium ($r = 0.031$; $p = 0.804$) or serum phosphorus ($r = -0.041$; $p = 0.75$).

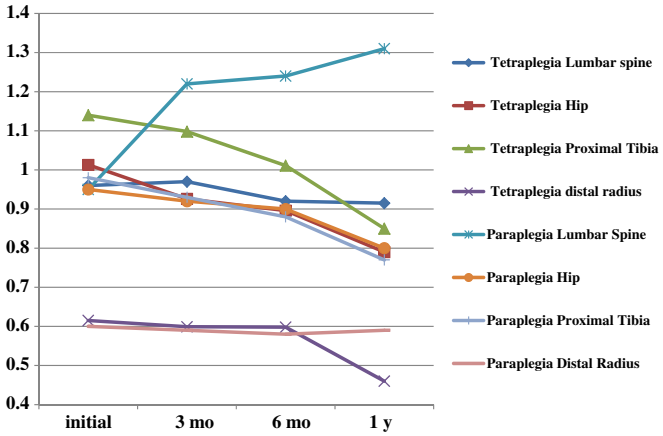

Figure 1. Graph showing trends of bone mineral density in the paraplegic group and the tetraplegic group at the initial, 3-month, 6-month, and 1-year follow-up periods.

Comparison of different groups

The comparison of the BMD in tetraplegic and paraplegic patients did not show any statistically significant differences at the lumbar spine, hip, and tibia. However, tetraplegic patients had a significantly lower BMD at the distal end of radius ($p < 0.05$; Table 4). There was no significant difference between the motor-complete (ASIA A and B) SCI patients and the motor-incomplete (ASIA C and D) SCI patients in terms of age ($p = 0.52$) and sex ($p = 0.18$).

The BMD in the motor-complete (ASIA A and B) SCI patients had significantly lower value in comparison with the motor-incomplete (ASIA C and D) SCI patients at the hip ($p < 0.05$) and the proximal tibial epiphysis ($p < 0.05$) at 1 year, whereas no significant difference was observed at the distal end of radius and the tibial diaphysis.

There was no significant difference in the BMD at 1 year between the nonoperative group and the operative group except that the BMD of the lumbar spine might be falsely high in those managed by pedicle screw fixation.

Discussion

Demineralisation after SCI had been documented in literature. Systemic factors known to regulate bone and calcium homeostasis may be altered after an episode of SCI. Hypercalciuria was reported after SCI, which would reduce with reambulation of the patients.[7,8] Plasma-ionised calcium elevated after SCI and lasted for 6 months

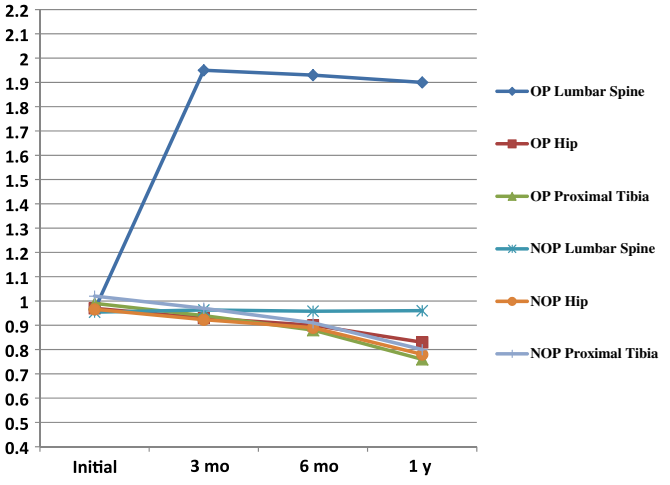

Figure 2. Graph showing trends of bone mineral density in operated (OP) and non-operated (NOP) spinal cord injury patients at the initial, 3-month, 6-month, and 1-year follow-up periods.

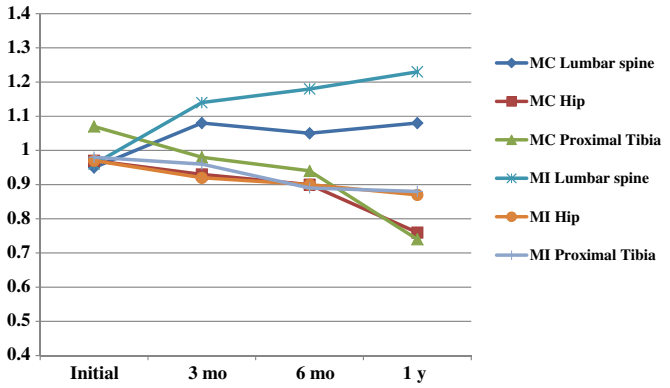

Figure 3. Graph showing trends of bone mineral density in motor-complete (MC; ASIA A and B) and motor-incomplete (MI; ASIA C and D) spinal cord injury patients at the initial, 3-month, 6-month, and 1-year follow-up periods.

Table 4
BMD in tetraplegic and paraplegic patients at 3-, 6-, and 12-month follow-ups

	Tetraplegics				Paraplegics			
	Initial	3 mo	6 mo	1 y	Initial	3 mo	6 mo	1 y
Lumbar spine	0.96	0.97	0.92	0.915	0.95	1.22	1.24	1.31
Hip	1.013	0.926	0.896	0.790*	0.95	0.92	0.90	0.80*
Proximal tibia	1.14	1.098	1.011	0.85*	0.98	0.93	0.88	0.77*
Tibial diaphysis	1.103	1.044	1.027	1.024	1.11	1.04	1.04	1.00
Distal tibial epiphysis	0.985	0.903	0.89*	0.802	0.98	0.94	0.90	0.78*
Distal radius	0.615	0.599	0.598	0.46*,†	0.60	0.59	0.58	0.59

BMD = bone mineral density.
* Statistical difference between the initial and 12-month values in the group.
† Statistical difference between the 12-month values of tetraplegics and paraplegics.

with the parallel increase in urinary calcium excretion. Increase in ionised calcium might result in suppression of parathyroid hormone and 1,25-dihydroxy vitamin D levels in the 4th to 12th month after SCI.[8–12] We did not find any hypocalcaemia or hypercalciuria during the 1st year after the injury in SCI patients. Burr and Nuseibeh[13] also found no significant differences in either serum calcium or phosphate values in paraplegic individuals. Markers of osteoblastic activity such as ALP level and osteocalcin were elevated in immobilisation osteoporosis, denoting increased bone formation.[14] Serum ALP is one of the most commonly used markers of bone formation, but the enzyme lacks sensitivity and specificity. Bergmann et al[15] reported high levels of ALP during the 1st year after injury in SCI individuals, which might reflect high levels of bone turnover. In our study, although the levels of serum ALP were found to be increased at 1-year post-SCI, they were within the normal range. There was no correlation between lower extremity BMD and serum ALP (Pearson correlation coefficient $r = 0.217$; $p = 0.076$); and between total-body BMD and serum calcium ($r = 0.031$; $p = 0.804$) or serum phosphorus ($r = -0.041$; $p = 0.75$). Demirel et al[16] also found no correlation between lower extremity BMD and serum ALP in patients with SCI ($r = -0.23$; $p = 0.27$). They found no correlation between total-body BMD and serum calcium ($r = 0.17$; $p = 0.27$) or serum phosphorous ($r = -0.24$; $p = 0.12$).

Twenty-four-hour urinary calcium and phosphorus levels were not significantly different at 1 year when compared with baseline values in our study, and this result was contrary to the findings of Kaya et al,[17] who reported a significant increase in the calcium level in 24-hour urine and calcium-to-creatinine ratio in spot urine samples in acute SCI patients; however, there was no significant difference between the subacute and chronic SCI patients.[17]

There was a significant decrease in BMD below the level of neurological injury with maximum decrease in the proximal tibial epiphysis at 1 year in our series, which was comparable with other prospective studies, showing bone loss after SCI.[3–5] We observed dissociated hip–spine demineralisation. The BMD of lumbar spine was well preserved, whereas a significant decrease in BMD at the hip was observed. This pattern of highly selective bone loss from the hip appeared to be unique compared with other endocrine causes of osteoporosis.[18] A significant decrease ($p < 0.001$) in BMD was observed at the tibia in our study. There was a 28% decrease at the upper tibial epiphysis and a 24% decrease at the distal tibial epiphysis (Table 3) for all patients at 1 year. Biering-Sørensen et al[19] reported that BMD of the femoral neck and shaft was 25% and that of the proximal tibia was ≥50% lower than normal values. In 1990, Biering-Sørensen et al[3] reported that BMD decreased after the injury, reaching new steady-state levels at 40–50% and 60–70% for the proximal tibia and femoral neck, respectively, at 2 years after the injury. Dauty et al[20] also showed a decrease of BMD below the level of injury of 41%.[14] This loss of bone mass was higher at the distal femur (−52%) and proximal tibia (−70%), which were the most common sites of fracture.[20] Wilmet et al[21] observed a rapid decrease of BMD in the paralyzed areas of approximately 4% per month during the 1st year in areas rich in trabecular bone and approximately 2% per month in areas containing mainly compact bone. However, Szollar et al[22] noted an increase in BMD of all age groups in the femoral regions immediately after injury (0–1 year after injury) that declined over time and stabilised at 10–19 years after injury. Modlesky et al[23] showed a 43% decrease in BMD at the proximal tibia after SCI, with a mean injury duration of 8.7 years.

Similar to our findings, Tsuzuku et al[24] and Demirel et al[16] found no significant difference in BMD of the lower extremities between paraplegic and quadriplegic individuals. A significant difference in the BMD of upper extremity was noted only in the tetraplegic individuals. Frey-Rindova et al[4] demonstrated trabecular and cortical bone losses of 19% and 3% in the radius of SCI patients with tetraplegia at 12 months. More bone loss at the distal end of radius in our patients (25%) compared with Frey-Rindova et al[4] might be explained by early rehabilitation and use of wheelchairs in their population. The amount of bone loss was also associated with the degree of post-traumatic immobilisation in other studies.[25,26]

The motor-complete (ASIA A and B) patients had significantly lower BMD than motor-incomplete (ASIA C and D) patients in the hip and proximal tibial epiphysis at 1 year in our study. Similar observations were also reported by other authors.[5,16,27] Individuals with incomplete SCI tended to lose less bone than individuals with complete SCI. The degree of mobility may be important: a cross-sectional study demonstrated that BMDs in SCI patients were positively correlated with their mobility with a mobility index ranging from complete paralysis to unlimited ambulation.[27] However, Kaya et al[17] could not find significant difference in BMD values between motor-complete and motor-incomplete patients. They also reported that the level and severity of SCI and spasticity did not significantly affect BMD values.

No significant difference was found in the BMD at 1 year between those who were managed conservatively and those who had some kind of operative intervention. An increase in lumbar spine BMD may be falsely high in those managed by pedicle screw fixation due to the implants and this site was excluded for comparison purposes. In addition, only few patients (22.1%) were managed surgically and could not prove any statistical significance.

Several factors may influence the loss of bone after SCI, but the exact sequence of these metabolic events is not fully understood. Some studies reported vascular changes caused by the autonomic nervous system dysfunction were important in the development of osteoporosis in SCI whereas immobilisation was only a minor

factor.[28,29] Others demonstrated that the degree of bone loss was correlated with degree of post-traumatic immobilisation and the time lapse after the injury.[25,26] A significant correlation between the cortical bone volume and muscle volume was demonstrated, which indicates that muscle activity plays a role in maintaining bone mass.[30] Initial bone mass losses were greater in trabecular than in cortical compartments.[1,4] Bone loss after SCI was site specific with the largest decrements in lower limbs.[1] Bone loss in the upper extremities was common in tetraplegia.[1] Individuals with incomplete SCI tended to lose less bone than those with complete SCI.[1,16] A number of measures, both prevention and treatment, were reported in the literature. Zehnder et al suggested the use of bisphosphonates such as alendronate over 24 months to decrease the bone loss.[31] Regular intensive loading exercise activity in early rehabilitation (tilt table and standing) could possibly alleviate the decrease of BMD in the tibia.[4] Bélanger et al claimed that increase in bone mass could be achieved with functional electrical stimulation-induced muscle strengthening.[32] Early mobilisation might reduce the bone loss in the acute stages after SCI.[33] Early wheelchair use for upper limbs, tilt table for gravity stimulation, and passive stretching were the other methods of decreasing the bone loss in SCI patients.

Conclusions

In acute SCI patients, there was a marked decrease in BMD in all metaphyseal sites below the neurological injury level with the maximum decrease in the proximal tibia during the 1st year. The markers of osteoblastic activity did not change much, but the decrease in BMD was influenced by the neurological recovery.

Conflicts of interest

The authors declare that they have no financial or non-financial conflicts of interest related to the subject matter or materials discussed in the manuscript.

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