

Copper deficit as a potential pathogenic factor of reduced bone mineral density and severe tooth wear

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Abstract

Summary The study evaluated if men and women with severe tooth wear were at increased risk of general bone loss. Enamel biopsies obtained from 50 subjects aged 47.5 ± 5 years showed decreased copper content, which was associated with reduced spine bone mineral density, suggesting deficits of this trace element contributing to bone demineralization, enamel attrition, and deteriorated quality of mineralized tissues.

Introduction The objective of this cross-sectional study was to assess associations between enamel trace minerals and bone mineral density (BMD) in severe tooth wear. We hypothesized that similar factors contributed to both the excessive abrasion of dental enamel and reduced BMD in subjects with tooth wear.

Methods Fifty patients aged 47.5 ± 5 years with severe tooth wear and 20 age-, sex-, and body mass index (BMI)-matched healthy volunteers with normal dental status were studied regarding dietary intakes of trace elements, serum and salivary copper (Cu), zinc (Zn), and calcium (Ca) concentrations, and serum PTH, osteocalcin, and hydroxyvitamin D levels. Tooth

wear was determined using clinical examination based on standard protocol according to Smith and Knight. In all subjects, acid biopsies of the maxillary central incisors were carried out to assess mineral composition of the enamel. Atomic absorption spectroscopy with an air/acetylene flame was used to measure Ca and Zn, and graphite furnace atomic absorption spectroscopy was used to analyze Cu content. BMD was examined using dual energy X-ray absorptiometry. **Results** Tooth wear patients had reduced lumbar spine, but not femoral, BMD relative to controls ($p < 0.001$). No differences were found in enamel Ca concentration and Zn content was slightly higher in tooth wear patients than in controls whereas Cu content was significantly decreased in the patients: 19.59 ± 16.4 vs 36.86 ± 26.1 $\mu\text{g/l}$ ($p = 0.01$) despite similar levels of Cu in serum and saliva. The differences were independent of serum 25-OH-D, osteocalcin concentrations or PTH either.

Conclusion Severe tooth wear is associated with reduced spinal BMD. Enamel in adult individuals with severe tooth wear is low in copper content. Therefore, further work is needed to determine whether copper plays a role in bone pathophysiology in these patients.

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Introduction

Teeth and bones are regarded the most mineralized tissues in humans. Several reports suggest association between tooth loss or small number of remaining teeth and reduced bone mineral density (BMD) [1–5]. There is also evidence of the effect of periodontal disease and osteoporosis in the elderly [6–11]. Furthermore, periodontal disease has also been reported an important and common coincidence of systemic bone loss in both women and men [12–16]. It has been

shown that the reduction of systemic BMD may be a risk factor for the development of tooth loss and oral health problems [2, 7, 17] suggesting possible cause–effect link, particularly in postmenopausal women with osteoporosis [13, 18, 19]. Some studies also show that dental status impairment related to osteoporosis may result from a considerable decrease of mandibular bone mass [20, 21], though the contributing factors remain unclear. Possible mechanisms may include tooth loss during ageing as a natural process secondary to the systemic bone loss; however, the age-related progressive dental decline may also co-exist with deficits in BMD [17, 21]. These associations are well recognized among the elderly but there are still limited data on such associations in younger age. Accelerated tooth wear appears one of the conditions affecting enamel, independently of age, so that it may occur in younger otherwise healthy people.

It is well known that tooth enamel is the hardest tissue in the human body. Although enamel does not have the typical structure of human bone, its chemical composition is similar. Hydroxyapatite and magnesium phosphate are building minerals essential for bone structure, quality, and resistance whereas some trace elements (i.e., zinc and copper) are very important for bone integrity and elasticity. Enamel is continuously affected by the process of wear. Although the tooth wear is recognized the physiological and irreversible phenomenon, there are individuals in whom this process of wear occurs dramatically faster and, if not treated, may lead to the complete destruction of stomatognathic system [22]. The cause of this acceleration of tooth wear is multifactorial as it is generally a combination of abrasion, attrition, and erosion. [23]. Thus, the processes of local demineralization and remineralization reflecting the erosion-attrition or erosion-abrasion play the key role in the clinical picture of wear [24–27].

As underlying mechanisms seem unclear in this condition, it is worth evaluating associations between tooth wear, skeletal status, and potential pathogenic pathways, focused on enamel composition. The effects of microelements such as zinc and copper on tooth demineralization and remineralization have been previously described [28, 29]. Zinc has been reported to reduce enamel solubility [29, 30]. It has been also suggested that zinc is incorporated into enamel during remineralization *in situ* despite a moderate level of an increase in zinc concentration [31]. Brookes et al. have further demonstrated that copper has a direct protective effect on the dissolution of enamel in acidic environment, being a major driving force for both caries and erosion [32]. By contrast, Koulourides observed an inhibition of enamel remineralization by Cu, presumably due to ionic interaction with the active enamel surface following demineralization [33].

Beyond an evident significance of calcium-phosphate in bone turnover, the role of micronutrients and elements, i.e., iron, magnesium, manganese, selenium, zinc, and copper is

also well known in bone metabolism [34–38]. Trace elements, in particular zinc and copper, are actively participating in enzymatic systems responsible for bone matrix turnover [39]. Zinc is a constituent of approximately 300 enzymes, including those essential for bone metabolism (bone alkaline phosphate) [40]. Copper is another trace element involved in bone metabolism as a cofactor of lysyl oxidase, one of the principal enzymes participating in collagen cross-linking. Animal studies suggest that Cu deficiency is associated with reduced bone strength and deterioration of bone quality leading to osteoporotic lesions [41].

Considering that enamel represents similar features, qualities, and mineralized components to bone tissues, we aimed to investigate possible associations between enamel mineral composition and BMD in adult patients with tooth wear. We hypothesized that both systemic bone loss (lower BMD) and excessive abrasion of dental enamel coincided in subjects with severe tooth wear.

Patients and methods

Participants

In this cross-sectional observational study, 50 participants (16 women, 34 men) aged 47.5 ± 5 years with advanced tooth wear were included. The patients were referred to the Department of Prosthetic Dentistry due to clinically apparent decrease of occlusal vertical dimension and a consequent reduced self-esteem of face aesthetics. On average, these subjects possessed 23 teeth. The control group consisted of 20 healthy volunteers aged 46.5 ± 6 years (eight women and 12 men), matched by body mass index (BMI), without signs of pathological tooth wear. They were asked to participate voluntarily in the study as they presented at the department to make minor prosthetic procedures relating only to a single tooth (e.g., crown or inlay). On average, the reference subjects possessed 27 teeth. All study participants demonstrated good general somatic condition, their own teeth were free of clinical signs of dental caries or periodontal disease. Tooth Wear Index (TWI) was used to categorize the participants.

The inclusion criteria for the studied patients were: the presence of widespread advanced tooth wear with multiple sites of exposed occlusal dentin (TWI on occlusal/incisal surface ≥ 2) and a considerable decrease in the occlusal vertical dimension (more than 4 mm measured in the anterior region), no significant periodontal bone loss or decay on their own teeth, no prior prosthetic rehabilitation attempting to treat the lost vertical dimension. Furthermore, the inclusion criteria for the whole group encompassed: absence of chronic metabolic, endocrine, renal, or gastrointestinal conditions, or prolonged medication known to affect bone metabolism, oral microflora, or the salivary flow rate. No history of clinically significant

fractures was reported in either of the groups. Patients who underwent prosthetic rehabilitation prior to recruitment were excluded. The participants were required to be available to be recalled multiple times during the duration of the study. Informed consent was obtained from each participant prior to confirmation of their eligibility for the study. The protocol was approved by the Ethical Committee of the Medical University of Białystok, Poland (approval # R-I-003/6/2006).

Methods

The dietary intakes of nutrients, including elements and vitamin D, were assessed with the validated 7-days food-frequency questionnaire based on the software DIETA 3, and the obtained data were compared to the national recommended daily intakes (RDIs). Both direct standardized interview-based questionnaire and medical records were utilized to accomplish medical history. Anthropometric measurements (body weight and height) were performed using electronic scale (Seca, Germany) and Harpenden stadiometer, whereas BMI was calculated using standard formula.

Dental examination and clinical procedures

All of the participants were clinically examined to evaluate tooth wear. Tooth wear was assessed according to the protocol of Smith and Knight [42]. The TWI was selected as an assessment measure because this method allowed to visually evaluate the level of wear. The maxillary central incisors of each subject underwent acid biopsies to assess the mineral composition of the enamel. The acid biopsy technique was used to determine calcium (Ca), zinc (Zn), and copper (Cu) contents in the tooth enamel [43].

The biopsies were taken between 10–11 AM, i.e., approximately 3 h after tooth paste use. All study participants were maintaining their customary habits regarding oral hygiene.

The enamel of the labial surface of the maxillary central incisors was cleaned with pumice, rinsed, and dried. Three analytical grade filter paper disks were placed in the middle part of the prepared surface. The diameter of the disks cut out of filter paper was 3 mm, and the paper was empty of any elements. Next, 1 μ l of 0.1 mol/l perchloric acid solution (HClO_4) was pipetted directly onto the middle of each of these disks. The acid was transferred using a micropipette (Eppendorf Varipipette 4710, Eppendorf-Nethler-Hinz, Germany). The acid was allowed to work on the enamel for 60 s. Immediately after removing the filter paper disks, the biopsy area was rinsed with distilled water and dried. Fluormex gel containing 1.25 % amino-fluorides (Chema, Poland) was applied to the enamel to promote re-mineralization. The biopsies were transferred to 1.5 ml sterilized, capped tubes (Safe-Lock, Eppendorf, Germany), then 1.5 ml of concentrated nitric acid and 0.5 ml of distilled water were added to

the samples which were mineralized using microwave mineralization (Uni Clever II, Plazmatronika, Poland). This method was used to completely degrade organic matter and convert it into inorganic substances. One well-qualified person performed all of the biopsies.

The amounts of Ca and Zn in the enamel bioplates were established using atomic absorption (AA) spectroscopy with an air/acetylene flame (Hitachi Model Z-500, Spectro, Germany). The concentration of each element was calculated using a calibration curve, and the curve for each element was constructed using the instrument. The concentration of Cu was measured using an electrothermic method with argon gas on the AA spectrometer, as calculated from the appropriate calibration curve. Reproducibility of the procedure was based on Ca, Mg, Zn, and Cu concentration values reported as the mean value from three tests. Twenty measurements were retested by one investigator who was familiar with the employed methods. The reproducibility agreement was found to be 90 %.

Saliva collection was made between 10.00 a.m. and 11 into sterile pot after chewing a stick of spearmint-flavored gum through 5 min. Flow rate, pH, bicarbonate, and element content analyses were performed within 15 min of saliva collection. The samples were mineralized with concentrated nitric acid in microwave mineralizer (Plazmatronika) and subsequently analyzed for Ca, Zn, and Cu concentrations using AAS method.

Bone mineral density measurements

Dual-energy X-ray absorptiometry (DXA) with the DPX Prodigy equipment (GE-Healthcare Lunar, Madison, WI, USA) was used to determine bone mineral density (BMD, g/cm^2) in the antero-posterior lumbar spine region (vertebral bodies L1–L4) and total femur. All scans and analyses were performed by an experienced certified clinical densitometrist (JK). The estimated reproducibility error in vivo (coefficient of variation) was 1.45 %, based on duplicate lumbar spine DXA examination performed in 24 subjects. Results were expressed as T-scores and were also compared to age- and sex-matched reference ranges and expressed as Z-scores for BMD according to the NHANES database provided by the manufacturer. The interpretation of the DXA results was based on current practice guidelines of ICSD.

Biochemical analyses

To determine biochemical parameters, 10 ml of blood taken for coagulum was used. The serum was frozen in the temperature -80 °C. The concentration of total calcium (mmol/L), inorganic phosphorus (mg/dL), total alkaline phosphatase (ALP; IU/L), osteocalcin (ng/mL), parathormone activity (iPTH; pg/mL), and hydroxyvitamin-D [25(OH)D; (ng/mL)]

were assessed. Ionized calcium (Ca^{+2}) level was evaluated in a 5-ml blood sample (Siemens lithium heparine syringe).

Statistical analysis

Statistical analysis of all of the studied attributes was carried out. In the case of quantitative traits, average and dispersion measures were used, i.e., arithmetic mean and standard deviation. The levels of studied attributes between the groups were compared using the *t* test. The strength of relationships between pairs of measurable parameters was determined using Pearson's correlation coefficient, and its significance was assessed using the *t* test for the correlation coefficient. The influence of potential factors on a measurable dependent variable, e.g., tooth wear indices, was assessed using analysis of variance. Differences and relationships were considered statistically significant at $p < 0.05$.

Results

Sixteen pre-menopausal women and 34 men aged 47.5 ± 5 years with advanced tooth wear were included in the study and compared with 20 age- and sex-matched healthy peers (12 men, eight premenopausal women) with normal dental status. Based on the clinical examination of 1,017 teeth from patients and 523 teeth from controls, a significant difference

in the TWI was found between the groups (Table 1). No associations were observed between TWI and gender, body weight, height, or BMI. There were no differences in anthropometric features between the groups, even if men and women were analyzed separately. Both male and female patients with severe tooth wear demonstrated lower BMD, particularly in the lumbar spine region, compared with their healthy references. This difference remained unaffected and significant after adjustment for sex. The difference in bone density was explicitly expressed in absolute values, T- and Z-scores, whereas the results remained within the normal range (Table 1). The patients did not differ from controls in calcium, phosphorus, zinc, copper nor in vitamin D consumption, although in general copper intakes were considerably lower in relation to RDI (Table 2). Furthermore, the dietary intakes of the above nutrients were not associated with the content of the respective elements in the enamel biopsies obtained from either of the groups.

The analysis of biopsies showed difference in copper amount in the enamel between the groups. No correlation between enamel copper and the degree of tooth wear was observed, however, significant difference was found in Cu content in the enamel between first and second levels of wear ($p = 0.04$). Tooth wear patients had significantly decreased copper content in comparison to controls despite normal salivary and serum concentrations of this element in the two groups (Table 3). Salivary concentrations of calcium, zinc,

Table 1 Characteristics of studied groups including anthropometric traits, dental status, and bone mineral density (BMD)

	Tooth wear patients ($n=50$)	Controls ($n=20$)	<i>P</i> values
Age (years)	47.5 ± 5	46.5 ± 6	NS
Female/male ratio	16/34	8/12	
Number of teeth (mean; range)	23 (14–28)	27 (26–28)	NS
Tooth Wear Index (TWI)	2.3 ± 0.5	0.8 ± 0.4	< 0.001
Height (cm)	173.5 ± 7.2	175.0 ± 11.1	NS
Weight (kg)	79.2 ± 9.8	80.4 ± 11.8	NS
Body mass index (BMI)	26.8 ± 3.9	26.2 ± 2.7	NS
Women			
BMD femur [g/cm^2]	0.93 ± 0.12	0.97 ± 0.13	NS
T-score for BMD femur	-0.45 ± 0.96	-0.17 ± 1.21	NS
Z-score for BMD femur	0.04 ± 1.13	0.22 ± 1.01	NS
BMD spine [g/cm^2]	1.08 ± 0.16	1.23 ± 0.22	0.02
T-score for BMD spine	-0.93 ± 1.33	0.24 ± 1.97	0.02
Z-score for BMD spine	-0.60 ± 1.59	0.42 ± 1.73	< 0.001
Men			
BMD femur [g/cm^2]	1.00 ± 0.12	1.02 ± 0.16	NS
T-score for BMD femur	-0.52 ± 0.89	-0.35 ± 1.24	NS
Z-score for BMD femur	-0.15 ± 0.82	-0.04 ± 1.18	NS
BMD spine [g/cm^2]	1.12 ± 0.11	1.21 ± 0.14	0.02
T-score for BMD spine	-0.92 ± 0.96	-0.08 ± 1.08	0.02
Z-score for BMD spine	-1.08 ± 0.96	-0.27 ± 1.01	< 0.001

Mean \pm SD are shown

NS not statistically significant

Table 2 Dietary intakes of calcium, zinc, copper, phosphates, and vitamin D in studied subjects

	Tooth wear patients (<i>n</i> =50)		Controls (<i>n</i> =20)		<i>P</i> values
	Daily amount	% of RDI	Daily amount	% of RDI	
Calcium (mg)	762.9±279.9	94	730.8±269.2	91	NS
Zinc (mg)	14.03±4.9	111	11.4±2.8	91	0.05
Copper (mg)	1.57±0.4	69	1.4±0.3	60	NS
Phosphorus (mg)	1,585±521	250	1,368±240	210	NS
Vitamin D (µg)	4.78±4.5		3.21±1.8		NS

Mean values ± SD and % of recommended daily intakes (RDIs) are shown
NS denote not statistically significant differences

and copper were similar in patients and controls. There were no differences in serum 25-hydroxyvitamin D, PTH activity, or bone formation marker (osteocalcin) between the two groups.

Discussion

Our study showed coincidence of reduced spine BMD and local enamel copper deficits in a group of patients suffering from a rare disorder: advanced tooth wear. This association was independent of dietary intake of copper or serum content of this element either. Some properties of saliva are considered an important biological factor affecting the rate of dental erosion, transporting ions, and mineralization balance [44, 45]; however, the low enamel copper in our patients was unaffected by salivary concentrations of this trace element. Considering other variables studied, i.e., bone formation markers, PTH, vitamin D status, or menopausal status in women, the decreased copper concentration may potentially play a role in the pathophysiology of mineralized tissues in human body. Whether there is a casual link between the Cu depletion in situ, susceptibility to lower BMD and advanced tooth abrasion, remains not fully understood.

Several studies in adult populations have documented associations between systemic bone loss in the development of tooth loss [4, 5, 7, 17, 46]. Resorption of tooth-supporting alveolar bone has been regarded as one of the responsible mechanisms [2, 17, 20]. Nonetheless, available data are inconsistent, and usually based on a self-reported tooth count. Most studies have focused on postmenopausal women, but a few reports have shown lower BMD being associated with the number of missing teeth also in men [12, 47]. Whereas certain studies in edentulous elder population have shown reduced BMD at the spine accompanied by higher BMD at the femoral neck [48], others have reported contrasting findings, i.e., lower femoral rather than spine BMD being associated with tooth loss [19]. These teeth–bones relationships relate usually to older people and prove clinical relevance of dental status in postmenopausal osteoporosis.

We extend this observation by demonstrating that the onset of dental disease with precocious rapid enamel abrasion in younger age may also coexist with decreased BMD. The DXA measurement, used in our study, does not allow insight into the structure or quality of bone, so that it is neither able to distinguish between cortical and trabecular bone loss nor between mineral and matrix deterioration. However, in this study, the reduction in BMD was detectable mainly in vertebral bodies, not in the femoral region, suggesting a negative effect on trabecular bone and enamel in individuals with tooth wear. The process affecting both enamel and bone tissue may result from either an earlier demineralization or inadequate bone growth, i.e., deterioration of microstructure. Genetic predisposition for tooth wear has not been yet described in the literature.

Possible underlying mechanisms of the two conditions may include disturbances in some trace elements leading, at least partly, to defective mineral and/or matrix composition in teeth and bones. Evidence supporting this view is available in animal studies reporting negative effect of low dietary intake of copper or its deficiency on bone matrix during growth, producing reduced bone strength and, thereby, the clinically apparent osteoporosis [49, 50]. Chronic exposure of growing rats to marginally low copper has been demonstrated to produce impaired mechanical strength, which predisposed the rats to bone fragility, independently of calcium/phosphate status. The explanation of this pathway focused on deteriorations in the collagen component of bone tissue attributable to defected intermolecular cross-linking which is essentially dependent on lysyl oxidase [51]. Others reported that deficiency of trace elements, including copper as the cofactor of this enzyme, may also play significant role in the pathogenesis of alcohol-induced reduction in bone mineral content in rats [52]. Absence of copper-dependent lysyl oxidase in humans has been clearly described as molecular cause of defective bone collagen in Menkes disease [36, 53]. Furthermore, results of animal studies have shown copper deficits in teeth and mandible being linked to experimental postmenopausal osteoporosis

Table 3 Comparison of calcium, zinc, and copper contents in enamel bioplates, saliva; serum concentrations of the elements, and serum levels of hydroxyvitamin D, PTH, and bone formation marker (mean values±SD are given)

	Tooth wear patients (n=50)	Controls (n=20)	P values
Enamel			
Ca [mg/L]	1.884±1.382	1.853±1.241	NS
Zn [mg/L]	0.142±0.041	0.084±0.022	0.05
Cu [µg/L]	19.861±13.171	36.673±22.661	0.01
Saliva			
Ca [mg/L]	61.691±36.851	70.771±57.572	NS
Zn [mg/L]	2.043±1.511	2.652±1.792	NS
Cu [µg/L]	114.644±78.362	78.321±61.691	NS
Serum			
Ca ⁺⁺ ionized (mmol/L)	1.21±0.07	1.20±0.06	NS
Ca (mmol/l)	2.36±0.10	2.36±0.11	NS
Zn [mg/L]	1.042±0.242	1.161±0.222	NS
Cu [mg/L]	0.741±0.205	0.713±0.212	NS
Phosphate (mg/dL)	3.16±0.51	3.08±0.55	NS
PTH (pg/mL)	58.69±28.31	56.56±22.04	NS
25(OH)D (ng/mL)	24.33±6.29	22.19±5.63	NS
Alkaline phosphatase (sALP) [IU/L]	55.14±15.81	62.35±17.59	NS
Osteocalcin (ng/mL)	19.87±6.05	18.75±4.62	NS

NS denote not statistically significant differences

in the whole skeleton [54]. These findings, although not directly relating to humans, suggest an important role of copper deficit in the impairment of mineralized tissues and, therefore, could support our hypothesis. Lichtenegger et al. reported an interesting constellation of biominerals in living organisms demonstrating high abrasion resistance, stiffness, and hardness of the jaws of *Glycera dibranchiata* due to the content and specific distribution of copper [55]. The investigators proved that copper-based biomineral atacamite formed in polycrystalline fibers was the key component enhancing an extraordinary resistance to abrasion despite generally sparse mineralization.

There are limited published data on the significance of trace elements in postmenopausal osteoporosis whereas none of the reports focused on bone status in younger population. Most of previous clinical studies provide evidence of beneficial role of copper and zinc in improvement of bone density and quality in both osteoporotic and healthy individuals, particularly found in cancellous bone, i.e., lumbar spine vertebrae [56–58]. Additional intake of trace elements was reported to positively and independently influence maintenance of spinal BMD in calcium-supplemented non-osteoporotic women [56]. Available data remain inconsistent, e.g., Mutlu et al. found considerably lower serum Zn and Mg levels, but not Cu concentration, in osteoporotic women, however, their study was based only on DXA examination of the femoral neck [59]. In our tooth wear patients, we report a site-specific relationship between decreased copper content in enamel and reduced BMD in the lumbar spine region. Interestingly, both patients and controls (even considering a limited number of the controls)

had suboptimal and similar copper intakes from diets, and did not differ in serum or salivary Cu concentrations, but only those with severe tooth wear demonstrated lower spinal BMD. This finding may reflect strictly local mechanisms of Cu deficits responsible for deleterious metabolism in hard tissues. Furthermore, this association may have appeared due to intensive bone turnover more pronounced in trabecular bones of vertebrae than in long bones. Both animal studies [49] and an interesting historical study using human bone samples obtained from autopsies [60] supported our observation.

We acknowledge that the excessive enamel erosion accompanied by unusual abrasive processes, both being core issues in tooth wear, could not be directly compared with porosity or trabecular thinning in bone, which appear essential in osteoporosis. Nevertheless, there is a lot of analogy regarding the final outcome indicating similar impairment of the quality and strength on the tissue level. A limitation of our study results from methodological aspects, i.e., the use of quantitative DXA method which is regarded only a surrogate of bone strength or quality. Thus, it is possible that bone biopsies, histomorphometry or high-resolution QCT of the skeleton, might detect true associations between trace element content and structure of bone, but those methods were unavailable. Moreover, the complexity of the interrelationships between micronutrients and their metabolic effects justifies certain controversies regarding the causal pathways and contribution of a single trace element to BMD, bone quality, or enamel structure and resistance. These limitations, however, do not detract from our main findings.

In conclusion, our data suggest that severe tooth wear is associated with an increased risk of reduced BMD in adults, with an effect expressed particularly in the lumbar spine. As enamel is low in copper content in the individuals with tooth wear, there is a possibility that defective metabolism of this trace element may contribute to coincidence of the two conditions. Nonetheless, larger prospective studies are needed to determine whether copper plays a role in bone pathophysiology in tooth wear patients and to elucidate whether systematic supplementation of copper would alleviate decline in BMD and precocious enamel abrasion.

Conflicts of interest None.

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