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Original Communication

The Effect of Zinc Deficiency and Supplementation on Elements in the Kidney Tissue of Ovariectomized Rats: Histopathologic Changes

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Abstract: The objective of the present study is to determine the effects of zinc deficiency in and zinc supplementation to ovariectomized rats on some elements in kidney tissue. The study included 40 Sprague-Dawley type adult female rats. The experimental animals were randomized into four groups with equal numbers as follows: Group 1: Control (10). Group 2: Ovariectomized control (10). Group 3: Ovariectomized + zinc supplemented (10). Group 4: Ovariectomized + zinc deficient (10). After the animals were decapitated at the end of the experiment, element levels were determined by Atomic Emission (ICP-AES) as mg/g/wet tissue for calcium, phosphate, zinc, aluminum, copper, iron, lithium, and manganese and µg/g/wet tissue for magnesium in the kidney tissue. Additionally, the tissue samples were subjected to a histopathologic assessment. An examination of the study results showed that ovariectomy significantly reduced calcium, phosphorus, and zinc levels, while zinc supplementation to the rats following ovariectomy restored the reduced element levels to normal (0.10 ± 0.03, 0.85 ± 0.16, 0.11 ± 0.03 vs 0.19 ± 0.06, 1.86 ± 0.18, 0.52 ± 0.05). Group 4, which was both ovariectomized and fed on a zinc-deficient diet, had significantly lower aluminum, copper, and lithium values. Calcification, inflammation, and sclerotic changes in group 4, the group which was fed on a zinc-deficient diet, were greater in comparison to other groups ($p < 0.05$). Results of the study suggest that ovariectomy + zinc deficiency leads to calcification, inflammation, and sclerotic changes in renal tissue and significantly reduces element levels, whereas zinc supplementation after ovariectomy restores the lowered element levels to normal.

Keywords: Kidney, ovariectomy, zinc supplementation, zinc deficiency, elements

Introduction

Zinc is known to be a key element required for growth in both humans and animals [1, 2]. There is a critical relation between zinc and growth. Also, zinc was reported to be a co-factor for specific enzymes in a number of metabolic events in the body [3]. Evaluation of references shows that both zinc and ovarian hormones are significant for renal function during menopause. Besides, it was reported that increased urinary zinc loss in post-menopausal women affected calcium levels in urine and consequently that there was a relation between zinc and calcium [4].

It has been established that zinc restriction in the fetal period impaired renal function in adult life [5, 6]. Similarly, zinc deficiency was shown to cause significant drops in serum calcium and phosphorus levels [7]. As opposed to zinc deficiency, zinc supplementation was reported to significantly improve element alterations and renal pathologies caused by its deficiency [7–9].

It was noted that increased chronic kidney diseases particularly after menopause in women resulted from the reduction in sex hormones [10]. Accordingly, estrogen was reported to have a kidney-protective effect [11]. However, it was also demonstrated that experimental estrogen treatment, particularly in post-menopausal mice, had a dose-dependent toxic effect on kidneys [12]. When the relation between estrogen and elements was considered, it was observed that estrogen deficiency increased zinc excretion [13], while estrogen treatment counteracted this effect in post-menopausal women [14].

Zinc was reported to have a remarkable ability to delay oxidative events [15]. Thus, it was suggested that zinc de-

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ficiency might cause an increase in free radical production or zinc supplementation might prevent free radical production [16].

Given the available literature data, both ovarian hormones and zinc seem to be undeniably significant for the body. The aim of the present study is to explore how 6-week zinc deficiency and zinc supplementation affect levels of calcium, phosphate, magnesium, zinc, aluminum, copper, iron, lithium, and manganese in kidney tissue and kidney histology in ovariectomized rats.

Materials and methods

Animal material and groups

This study was conducted at the Experimental Medicine Research and Application Center of Selcuk University after being approved by the Ethics Committee of the concerned institution. The study included 40 Wistar albino type rats weighing 250–260 g on average. All rats were kept and fed in rooms with controlled light and temperature conditions.

Group 1 (n = 10): The group was not subjected to any procedure.

Group 2 (n = 10): The group was on a normal diet after being ovariectomized under general anesthesia.

Group 3 (n = 10): The group was supplemented with intraperitoneal zinc (3 mg/kg/day) for 6 weeks after being ovariectomized under general anesthesia.

Group 4 (n = 10): The group fed a zinc-deficient diet (0.65 ppm zinc/g diet) for 6 weeks after being ovariectomized under general anesthesia.

In order to minimize zinc contamination, the experimental animals were fed in special steel cages that were cleaned daily by washing. The feed was given in special steel bowls and water in glass feeding bottles. Both zinc-deficient and normal forms of animal feed were prepared in Korkuteli Feed Supplement Industry Factory (in Korkuteli).

Zinc sulfate administration

After being dissolved in distilled water, zinc sulfate was administered in 0.5 mL physiologic serum in 3 mg/kg/day intraperitoneal injections. Zinc sulfate injections were given at the same hour of the day (09.00 a.m.) for 6 weeks.

Ovariectomy

The rats were injected with 60 mg/kg ketamine and 5 mg/kg rompun to induce general anesthesia. After the hair on the back of the rats was shaved, proper asepsis and antisepsis were ensured using betadine. The rats were put into ventral position, and the skin was incised at the 1/3 upper point of the distance between the tail and the mid-dorsal area. After the subcutaneous tissues were released, spinal muscle was reached. Peritoneal cavity was entered through the back wall muscles of the abdomen. Ovaries were removed together with the fatty tissue. Ovaries were first cleaned off the fatty tissue, then clamped, tied, and cut. After checking for bleeding, the other organs were put back into the peritoneal cavity. Lastly, the muscle was sutured with 2/0 chrome catgut and the skin with 2/0 silk [17].

After the animals were decapitated at the end of the procedures, kidney samples were taken to determine the levels of some elements.

Analyses of calcium, phosphate, magnesium, zinc, aluminum, copper, iron, lithium, and manganese levels in the kidney tissue

Samples of renal tissue were put into capped polyethylene tubes washed with NHO_3 and deionized water to prevent contamination. Tubes were stored at –35 °C until the day of analysis. Wet weights of the renal tissues were recorded. Concentrated H_2SO_4 and HNO_3 were added to the samples (g tissue / mL H_2SO4 / mL HNO_3 = 1/1/10). Samples were then left to wait in a closed-system microwave oven (CEM – Marsx5) at 170 psa pressure and 200 °C for 20 min, deionized water was added to obtain the final volume of 25 mL. After a maximum waiting period of 30 min, samples were read. The analyses were conducted using the Atomic Emission (ICP-AES) device in the Department of Soil Science of S.U. Faculty of Agriculture [18]. Calcium, phosphate, zinc, aluminum, copper, iron, lithium, and manganese values in the kidney tissue were calculated as mg/g wet tissue and magnesium values were obtained as μg/g wet tissue.

Histological examination

Kidney tissue samples taken from the animals at the end of the study were decalcified, stained with hematoxylin/eosin, and examined under a light microscope at 40×. Histological results including calcification, inflammation, and sclerotic changes in the renal tissue were examined. Hematoxylin/eosin is a routine staining method used in pathology and histopathology laboratories. As a general tissue stain it is used to discern nucleus and cytoplasm. This staining method is preferred for mice and rat experiments. MedLine scanning showed that much more research is present on rat tissue samples and hematoxylin/eosin staining. For this reason we have chosen this method to determine the histological changes in the kidneys of our study. [19].

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Statistical evaluations

The statistical evaluation of the results was carried out using computer software. Arithmetic means and standard deviations for all parameters were calculated. Variance analyses were used to identify the differences between groups. Bonferroni post hoc test was employed to compare group means in the statistically significant analysis results. Differences with $p < 0.05$ were accepted as significant.

Mann-Whitney U test was used in the statistical analysis of histology results, which were evaluated by comparing median values. Level of significance was set at $p < 0.05$.

Results

Calcium, phosphorus, magnesium, and zinc levels in the kidney tissues of study groups are presented in Table I. Examination of magnesium levels in the kidney tissue shows that neither ovariectomy (OVX) nor zinc deficiency nor post-OVX zinc supplementation had any effect on this parameter.

When calcium, phosphorus, and zinc values were addressed, OVX was found to cause a significant decrease in all these parameters ($p < 0.05$). However, 6-week zinc supplementation following ovariectomy elevated the reduced element levels back to control values ($p < 0.05$). In group 4, zinc deficiency together with OVX caused the OVX-induced decrease in element values to become more marked ($p < 0.05$). A comparison of the element levels demonstrated that groups 1 and 3 had the highest and group 4 had the lowest element levels.

When kidney tissue aluminum values were examined, it was seen that this parameter remained unaffected by OVX and zinc supplementation, but dropped significantly as a result of zinc deficiency and OVX ($p < 0.05$; Table II). Copper levels in the renal tissue fell after OVX ($p < 0.05$), but neither zinc deficiency nor zinc supplementation affected the reduced copper levels (Table II). Iron levels in kidney tissue increased after OVX ($p < 0.05$) and did not differ significantly from control values as a result of zinc supplementation or deficiency. While lithium values were not affected by OVX or zinc supplementation, this parameter was found to decrease significantly in the ovariectomized group which was on a zinc-deficient diet ($p < 0.05$). A comparison of the

Table I. Calcium, Phosphorus, Magnesium, and Zinc levels in the Kidney Tissues of Study Groups

Groups	Calcium (mg/g/ wet tissue)	Phosphorus (mg/g/ wet tissue)	Magnesium (mg/g/ wet tissue)	Zinc (mg/g/ wet tissue)
C	0.21±0.05[a]	1.84±0.15[a]	32.44±0.87	0.47±0.07[a]
Ovx	0.10±0.03[b]	0.85±0.16[b]	31.58±0.11	0.11±0.03[b]
Ovx-Zn S	0.19±0.06[a]	1.86±0.18[a]	33.98±0.14	0.52±0.05[a]
Ovx-ZnD	0.05±0.05[c]	0.51±0.11[c]	31.87±0.96	0.05±0.05[c]
P	0.05	0.05		0.05

C: Control; Ovx-C: Ovariectomy; Ovx+Zn S: Ovariectomy + Zinc supplementation; Ovx-Zn D: Ovariectomy + Zinc deficiency
* Means with different superscripted letters in the same column are statistically significant ($p < 0.05$). "a > b > c"

Table II. Aluminum, Copper, Iron, Lithium, and Manganese Levels in the Kidney Tissues of Study Groups

Groups	Aluminum (mg/g/ wet tissue)	Copper (mg/g/ wet tissue)	Iron (µg/g/ wet tissue)	Lithium (mg/g/ wet tissue)	Manganese (mg/g/ wet tissue)
C	6.41±2.13[a]	206.54±66.74[a]	494.30±239.4[b]	0.38±0.10[a]	0.04±0.01[a]
Ovx	6.23±2.86[a]	131.43±66.48[b]	705.40±241.70[a]	0.42±0.21[a]	0.03±0.01[b]
Ovx-Zn S	6.37±2.92[a]	144.47±56.67[b]	610.6±163.8[b]	0.41±0.11[a]	0.03±0.01[b]
Ovx-Zn D	2.72±2.22[b]	162.67±68.05[b]	589.8±142.0[b]	0.27±0.06[b]	0.03±0.01[b]
P	0.05	0.05	0.05	0.05	P

C: Control; Ovx-C: Ovariectomy; Ovx+Zn S: Ovariectomy + Zinc supplementation; Ovx-Zn D: Ovariectomy + Zinc deficiency
* Means with different superscripted letters in the same column have statistical significance ($p < 0,05$). "a > b"

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kidney-tissue manganese levels revealed a significant decrease resulting from OVX in this parameter ($p < 0.05$). Similar decreases in manganese levels were observed in the zinc-supplemented and zinc-deficient ovariectomized groups, relative to the control group ($p < 0.05$; Table II).

Histological results including calcification, inflammation, and sclerotic changes in the kidney tissue were evaluated. There was no significant difference between the control group, which was not subjected to any procedure (group 1), and the zinc-supplemented ovariectomized group (group 3) in terms of calcification, inflammation, and sclerotic changes (Figures 1, 3). However, these values in the ovariectomized control group (group 2; Figure 2) were found to be higher than their counterparts in groups 1 and 3 and lower than their counterparts in group 4 (Figure 4; $p < 0.05$). Calcification, inflammation, and sclerotic changes in group 4, the group which was fed a zinc-deficient diet, were greater in comparison to other groups ($p < 0.05$) (Table III).

Discussion

An overall assessment of the study results indicates that both ovariectomy and zinc supplementation/deficiency in rats significantly affect the distribution of calcium, phosphorus, and zinc in kidney tissue. Zinc deficiency and supplementation, in particular, brought about changes in the quantity of the concerned element in the kidney tissue, parallel to the deficiency or supplementation. When relevant literature is reviewed, it is seen that the effect of OVX on bone metabolism of rats is more commonly studied [20–22].

When calcium values in the renal tissue were examined, it was seen that this parameter dropped as a result of OVX. Calcium loss and urinary calcium excretion triggered by OVX have been reported [23]. Zinc deficiency influences the function of zinc transporters. Consequently, it also impacts the storage, use, and renal excretion of zinc [24]. Zinc deficiency reduced the quantity of Zn in kidney tis-

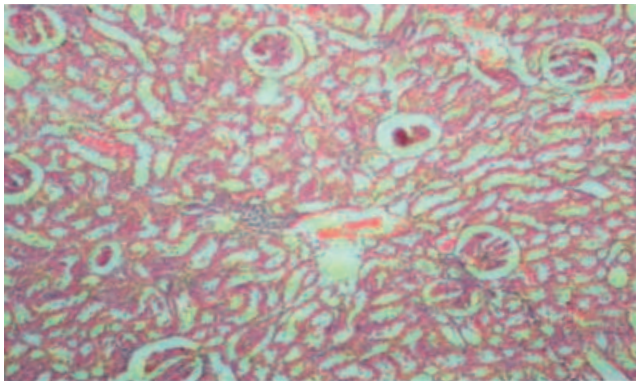

Figure 1. Normal rat kidney tissue.

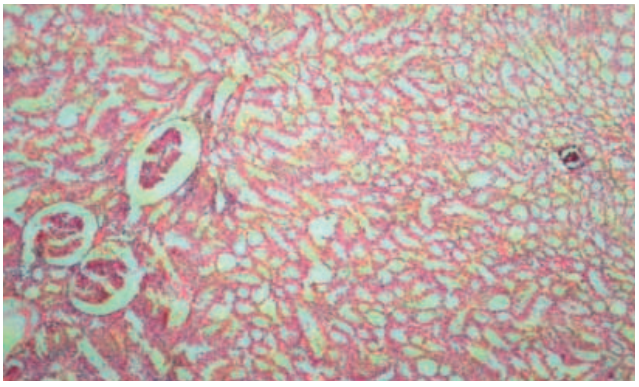

Figure 2. Kidney tissue of ovariectomized rat (mild calcification, inflammation, sclerotic changes).

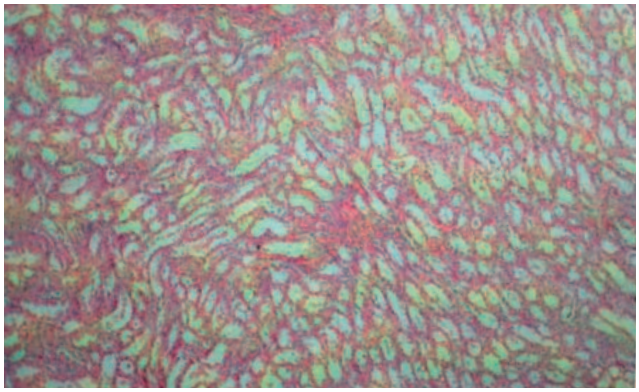

Figure 3. Kidney tissue of ovariectomized and zinc-supplemented rat (not different from Figure 1).

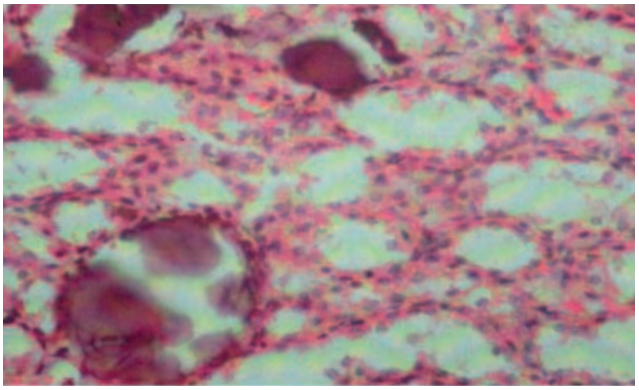

Figure 4. Kidney tissue of ovariectomized rat fed on a zinc-deficient diet (severely increased calcification, inflammation, and sclerotic changes).

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Table III. Histological Changes in the Kidney Tissues of Study groups

Groups	Calcification (Median value)	Inflammation (Median value)	Sclerotic changes (Median value)
C	1.000[c]	1.000[c]	1.000[c]
Ovx	3.000[b]	3.000[b]	3.000[b]
Ovx-Zn S	1.000[c]	1.000[c]	1.000[c]
Ovx-Zn D	5.000[a]	5.000[a]	5.000[a]
P	0.05	0.05	0.05

C: Control; Ovx-C: Ovariectomy; Ovx+Zn S: Ovariectomy + Zinc supplementation; Ovx-Zn D: Ovariectomy + Zinc deficiency
* Means with different superscripted letters in the same column are statistically significant ($p < 0{,}05$). "a > b > c"

sue. Zinc supplementation, on the other hand, restored the impairment resulting from zinc deficiency [25]. Zinc supplementation can produce different effects depending on the organ and peripheral tissues [26]. In our study, kidney tissue calcium levels were seen to drop by about 50 % due to OVX. There are several studies reporting OVX-associated decreases in serum calcium levels [7, 27–29]. The decreases in kidney tissue calcium levels in our study are parallel to the changes in the serum calcium levels. In what may be considered the second part of our study, the effect of zinc supplementation and deficiency on the calcium alteration in kidney tissue was explored (groups 3 and 4). It was found that zinc supplementation restored the calcium decrease in the renal tissue, while zinc deficiency together with OVX rendered the reduction in calcium levels more marked. Similar results have already been reported, though not in the kidney tissue [but serum], and our results are parallel to these previous reports [7]. The decrease in tissue calcium may have resulted from an increase in urinary calcium excretion. In the same vein, there are studies stating that urinary calcium excretion increased with OVX [30]. A second reason for the change in calcium levels may be the change in the tissue distribution of the element. In fact, it was already reported that calcium in the uterus tissue increased after OVX, and calcitonin and inorganic phosphate, parameters associated with the calcium metabolism, displayed significant changes [20]. Oophorectomy increases bone loss, and the bone mineral loss is caused by the temporary increase in the excretion of calcium through the gastrointestinal tract and kidneys [31, 32]. Calcium and phosphorus levels are known to decrease as a result of OVX [27]. Conversely, there are results showing that serum calcium and phosphorus levels increase after OVX [33].

An examination of the effect of zinc supplementation and zinc deficiency together with OVX on phosphorus levels in the kidney tissue in our study demonstrated that this parameter decreased significantly as a result of OVX, and this decrease became more evident in zinc deficiency. However, 6-week zinc supplementation significantly reinstated the reduced kidney tissue phosphorus levels, which were elevated back to control levels. Phosphorus resorption from the kidney is regulated by the effect of parathyroid hormone on the sodium-phosphorus co-transporter mechanism, and in the context of this regulation, estrogen was claimed to be involved in renal phosphorus retention [34]. The change in the renal phosphorus levels may be attributed to the deficiency of ovarian hormones. There are studies, parallel to ours, reporting reduced phosphorus levels in association with OVX [7, 28]. It should be noted that decreases caused by OVX in the kidney phosphorus levels were reversed by zinc supplementation, which restored the concerned levels to normal, and this result is consistent with the results of previous studies [7].

When magnesium levels in kidney tissue were investigated, it was seen that this parameter remained unaffected by OVX or zinc supplementation and deficiency. It was reported in a previous study that urinary magnesium loss increased as a result of OVX [23]. However, there are also studies reporting that there was no OVX-associated change in the magnesium levels, and our results are parallel to the results of these studies [7, 28]. This shows that neither ovarian hormones nor zinc supplementation/deficiency have any effect on the magnesium levels in the kidney tissue.

An evaluation of kidney tissue aluminum values showed that this parameter was not influenced by OVX or zinc supplementation. There is a limited number of studies exploring the relation between kidney tissue and aluminum [30]. It was reported in a previous study that estrogen replacement affected aluminum excretion from the kidney, and accordingly, the changes in ovarian hormones modified the element distribution in tissues [30]. In our study, zinc supplementation following OVX did not affect aluminum levels in the concerned tissue, while zinc deficiency induced after OVX reduced kidney aluminum values. This

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difference in the results may be explained by the duration of supplementation.

When the effect of zinc supplementation and deficiency together with OVX on kidney tissue copper and manganese levels was examined, it was found that these two elements showed similar changes. OVX attenuated the levels of the former, which were not affected by either zinc supplementation or deficiency. The reduction observed in copper levels due to estrogen deficiency in previous studies supports our results [35, 36]. It was argued that OVX affected manganese and consequently MnSOD activity [37, 38]. In our study, manganese values in the kidney tissue were established to decrease significantly as a result of OVX. Thus, our results are similar to those of previous studies [27]. This decrease may be explained by increased MnSOD activity, as MnSOD activity was reported to increase after OVX [37].

Concerning the effect of OVX together with zinc supplementation and deficiency on iron levels in kidney tissue, it was found that the amount of this element in kidney tissue increased significantly after OVX. In a study where the effect of sex hormones on iron was addressed, it was reported that the levels of this element in the blood dropped as a result of estrogen deficiency [36, 39]. However, it was seen that 6-week zinc deficiency/supplementation following OVX did not produce any significant change in the kidney tissue iron levels. The difference in these results may stem from the OVX-induced changes in the blood and tissue levels of this element.

An evaluation of lithium levels in kidney tissue revealed that the level of this element was not affected by OVX and zinc supplementation, but decreased significantly as a result of OVX + zinc deficiency. However, it was reported in the studies addressing ovarian hormones and lithium that this element acted through reduced estrogen receptors in the uterus [40].

As for the last parameter examined in our study, namely zinc, it was established that levels of this element in the kidney tissue fell markedly after OVX. However, as expected, this decrease was significantly reversed by 6-week zinc supplementation which restored zinc levels to those of control subjects. There are studies reporting reduced zinc values in OVX [28–30]. Thus, our results are consistent with those of previous studies. Reduced serum estrogen levels impair renal function [41]. Besides, 17-β-estradiol can act on kidney function by exercising a dose- and time-dependent effect on MnSOD and extracellular SOD [ecSOD] activity [42]. Such impairment in the normal function of kidney tissue may have affected the element distribution in the tissue.

Lastly, histopathological changes in kidney tissue were examined. The elevated rate of calcification and inflammation, as well as sclerotic changes observed in kidney tissue samples of group 4, the group on a zinc-deficient diet, shows that zinc deficiency causes damage to kidney tissue. In a study including rats that had streptozotocin-induced diabetes and were fed a zinc-deficient diet, zinc deficiency significantly increased calcium-phosphorus excretion in comparison to the diabetic rats on a normal diet, and accordingly, the former group had greater bone injury than diabetic controls. Interestingly, bone destruction observed in diabetic control animals could be reversed by insulin administration, whereas the damage to the bones could not be repaired by insulin administration in diabetic rats on a zinc-deficient diet [43].

Considering the elevated free radical levels in ovariectomized rats [44], increased urinary zinc excretion after menopause [13, 14], and the ability of zinc to block free radicals [15], it seems inevitable that there is a relation between zinc and kidney tissue in the menopausal period. However, it is certain that menopause and/or ovariectomy disturb the body's zinc balance and this event affects renal zinc levels. Corruption of renal function may be caused by changes in renal tissue elements.

Conclusion

The results of our study indicate that ovariectomy reduces calcium, phosphorus, and zinc levels in the kidney tissue of rats and this decrease is rendered more evident in the case of zinc deficiency. Six-week zinc supplementation following ovariectomy, on the other hand, restores the altered element distribution in the kidney tissue.

Conflict of interest

The authors declare that there is no conflict of interest.

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