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ORIGINAL ARTICLE

Possible Correction of Thiazide-Induced Hypokalemia with Co-Administration of Date Palm Fruits with Hydrochlorothiazide in Rats

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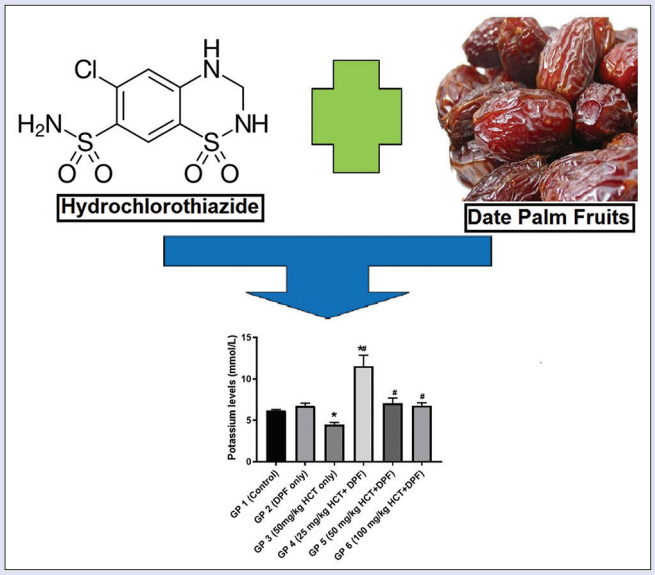
ABSTRACT

Background: Thiazide diuretics are one of the most effective, least expensive antihypertensive medicines, however, they are associated with hypokalemia, which can complicate the outcome of care among hypertensive patients. The concurrent administration of a potassium-rich food such as date palm fruits (DPFs) could be an attractive strategy in ameliorating thiazide-induced hypokalemia. The objective of this preliminary study was to investigate the effect of concurrent administration of DPF with hydrochlorothiazide (HCT), a thiazide diuretic on serum potassium level and lipid profile. **Materials and Methods:** Thirty-six rats were used for this study and were divided into 6 experimental groups comprising control (normal saline), DPF only, HCT, 25 mg/kg plus HCT, 50 mg/kg plus HCT, and 100 mg/kg plus HCT. Animals were dosed daily for 4 weeks and at the end of the experiment, blood samples were collected and allowed to cloth. Subsequently serum were analyzed for potassium levels and lipid profile. **Results:** Results showed that DPFs produced significant weight loss compared to the control and HCT only groups. Furthermore, serum potassium levels were increased abolishing hypokalemia produced by HCT in all the combination treatments. Total cholesterol, triglyceride, and low-density lipoprotein levels were all attenuated by concurrent treatment with DPFs and HCT. **Conclusion:** Therefore, the present study demonstrates that co-administration of DPFs with HCT restored serum potassium levels in rats and hence alleviated the attendant HCT-induced hypokalemia.

Key words: Date palm fruits, hydrochlorothiazide, hypokalemia, lipid profile, serum potassium

SUMMARY

- Thiazide diuretics are one of the most frequently used in the chronic management of hypertension in Saudi Arabia and worldwide. However, thiazide-induced hypokalemia is a potentially serious adverse side effect which can complicate the outcome of care among hypertensive patients. Date palm fruit (DPF) is a rich source of several minerals including potassium. The concurrent administration of a potassium-rich food such as DPF, which is widely cultivated and consumed in the Middle East, is a potentially attractive strategy to prevent thiazide-induced hypokalemia. The study was to evaluate the effect of concurrent administration of DPF with a thiazide diuretic (hydrochlorothiazide [HCT], HCZ) on serum potassium level. Results from the present study showed that concurrent administration of DPF with HCT normalized serum potassium levels in rats, thereby mitigating HCT-induced hypokalemia. In addition, co-administration of HCT with DPF produced significant reduction in total cholesterol, triglyceride and low-density lipoprotein-cholesterol levels, indicating a potential lipid-lowering activity.



Abbreviations used: LDL-C: Low-density lipoprotein-cholesterol; KCl: Potassium chloride; SD: Standard deviation; ALLHAT: Antihypertensive and lipid-lowering treatment to prevent heart attack trial.

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INTRODUCTION

Hypertension is a chronic noncommunicable disease with a rising prevalence and daunting public health challenge worldwide.[1] It is a consistent major contributor to high disease burden, explosion of morbidity and mortality due to negative cerebrovascular and cardiovascular events, and enormous direct and indirect health-care costs.[2] Therefore, blood pressure control is a strong determinant of risk reduction among hypertensive patients.[3,4]

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Hypertension is endemic in Saudi Arabia, particularly in the Eastern Region, and chronic management with varieties of the available antihypertensive medicines in addition to lifestyle and dietary interventions is the major therapeutic intervention.[5] Published studies show that thiazide diuretics are one of the most frequently prescribed antihypertensive medicines worldwide.[6] Thiazides have been shown by several studies to be an effective, safe, and most easily affordable of the antihypertensive medicines available. Thiazides have consistently been shown to achieve superior reduction in negative cardiovascular events including stroke, coronary artery diseases, and cardiac failure. However, hypokalemia is one of the adverse side effects frequently associated with the use of thiazides.[7] In addition, other studies have reported an increased incidence of hypokalemia-associated new-onset diabetes mellitus with thiazide diuretics.[8,9] In addition, thiazide-induced hypokalemia is also contributory to increased mortality due to ventricular ectopy.[10] Varieties of therapeutic strategies including the use of potassium supplement or combination with potassium-sparing antihypertensive medicines are currently in use to prevent thiazide-induced hypokalemia. However, there is currently no previous report of the potential beneficial effects of concurrent administration of potassium-rich food such as date palm fruits (DPFs) in correcting thiazide-induced hypokalemia. DPF *Phoenix dactylifera* L. is a major indigenous fruit that is widely cultivated and consumed in the Middle East in general and Saudi Arabia in particular. Based on previous reports on DPFs, the study revealed that it contains antioxidant flavonoid, which possesses hepatoprotective, nephroprotective, and anti-inflammatory properties.[11] Other studies reported that date syrup was found to be useful in the treatment of several diseases such as bacterial infections, angiogenesis as well as showing significant neuroprotection.[12]

DPF is a rich source of many components including carbohydrates (44%–88%), protein (2.3%–5.6%), minerals (0.1–916 mg/100 g), vitamins and dietary fibers (6.4%–115%), polyphenolic compounds, and antioxidants.[13] Date fruits also contain several minerals including potassium. The percentage content of minerals in dried dates varies from 0.1 to 916 mg/100 g, with the potassium concentration as high as 0.9% in the flesh of date fruits.[14] The average potassium concentration in 100 g of DPFs (6–7 date fruits) is 656 mg.[15] The widespread consumption of DPFs in Al-Hassa, and is the most important date-growing region in Saudi Arabia. The preliminary investigation of the potential impact of the co-administration of DPF with thiazide on serum potassium level using an animal model is warranted and will provide an initial insight and significant addition to literature upon which future clinical studies in this research area can be premised. Therefore, the objective of this preliminary study is to investigate the effect of concurrent administration of DPFs with a thiazide diuretic (hydrochlorothiazide [HCT]) on serum potassium level in an animal model.

MATERIALS AND METHODS

HCT (hydrochlorothiazide) (purchased from Sigma-Aldrich, St. Louis, MO, United States), date palm fruit (purchased from Al-Hassa local market and was identified by a pharmacognosist in King Faisal University, Saudi Arabia. Standard potassium solution 1000 mg L^{-1} was purchased from Scharlau (Sentmenat, Spain). Analytical grade nitric acid was procured from Sigma-Aldrich (St. Louis, Germany). Serum potassium level was determined using atomic absorption spectrophotometer (AA 6300, Shimadzu Corporation, Japan) potassium hollow cathode lamp. Lipid profile of plasma was determined using Roche Cobas 500 analyzer (Roche, Mannheim, Germany).

Study design: Controlled experimental design

Thirty-six rats were used for this study and they were acclimatized in cages with food and water *ad libitum*. The animals were kept at the temperature and humidity-controlled room in a 12-h light-dark cycle. International protocol was followed in the treatment of the experimental animals and also, according to the Deanship of Scientific Research, King Faisal University ethical rules as approved (KFU-REC-/2021-06-09). Dosages of HCT were adopted modified according to the methods of Zhou *et al.*,[16] and Jalalpure and Gadge,[17] while those of DPFs were modified methods of from previous study[18] and Habib and Ibrahim.[19] After acclimatization, the animals were divided into six treatment groups. Groups I and II were the control and 100 g unprocessed date fruits obtained from Al-Hassa, respectively. Group III received 50 mg/kg of HCT, while Group IV was treated with a combination of 100 g of DPF and 25 mg/kg of HCT. Group V animals were treated with a combination of 100 g of DPF and 50 mg of HCT, while Group VI was treated with 100 g of DPF and 100 mg/kg of HCT. All animals received daily doses for 4 weeks and thereafter blood samples were collected, and the extracted serum was stored at-85°C until analyzed.

Determination of serum potassium levels

The method of Yusuff *et al.*[18] was used for this analysis. Serum potassium level in the experimental rats was determined using atomic absorption spectrophotometer equipped with potassium hollow cathode lamp, high sensitivity nebulizer and the air-acetylene flame. The wavelength of the cathode lamp was set at 766.5 nm to measure absorption. Double distilled water prepared on a daily basis was used for the determination. The standard potassium solutions (0.1–2.0 ppm) were prepared by diluting the 1000 mg L^{-1} potassium solution with 1 mL of 1 N nitric acid, and the calibration curve was constructed by least square regression analysis of absorption against the concentration of calibration standards. One milliliter of 1N nitric acid was added to the serum sample (0.2 mL) and diluted with double distilled water, to get the concentration in the range of calibration curve. The atomic absorption was determined for the serum samples and concentration was calculated with the linear equation.

Serum lipid profile determination

Lipid profiles including serum total cholesterol, triglycerides, high-density lipoprotein-cholesterol, and low-density lipoprotein-cholesterol (LDL-C) were analyzed by using Roche Cobas 500 analyzer system in the Department of Laboratory Medicine using enzymatic colorimetric assays from Roche.

Statistical analysis

Data obtained from this study are expressed as mean ± standard deviation and were analyzed using the GraphPad Prism software version 9.2 (San Diego, CA, USA). Comparisons between the control and treatment groups were made using one-way analysis of variance at 95% confidence interval. Differences between the groups were computed using Tukey's multiple comparisons test. Statistical significance was considered at $P < 0.05$.

RESULTS

Weight changes after 4 weeks of treatments

The mean body weights of experimental animals after 4 weeks of treatments are presented in Table 1. Results revealed that while the control group mean weight after 4 weeks increased to 199.25 ± 8.02 from 186.75 ± 8.99 g, with a weight gain of 12.5 g, the DPF only group had a mean weight decrease, from 141.5 ± 14.52 to 115.75 ± 11.23 g, having lost

a total of 25.75 g. Generally, our observation from the results obtained shows that all combination treatments of DPFs with HCT produced significant weight loss ($P < 0.05$) compared to HCT only treatment ranging from 24 to 33.5 g.

Therefore, we can attribute the observed weight loss to be due to concurrent use of DPFs. Analyzing the weight gain or loss in all the treatment groups [Figure 1], the control gained 12.5 g, whereas the HCT only group gained 18 g. The trend in weight changes was consistent with all the treatment combinations showing significant ($P < 0.05$) weight loss.

Serum potassium level determination

As shown in Figure 2, administration of HCT to experimental rats showed a significant potassium loss ($P < 0.05$) compared to control. The DPF only group, however, showed a non-significant increase compared to the control. Among the combination groups, it showed that serum potassium levels were increased significantly ($P < 0.05$) in all the groups. However, 25 mg/kg plus DPFs had the highest potassium level increase. Looking at the results of the combination treatment groups, it appeared to exhibit dose-dependent effects with 100 mg/kg plus DPFs showing level similar to control, both showing significantly different levels when compared to the HCT only treatment group [Figure 2].

Table 1: Effect of hydrochlorothiazide and hydrochlorothiazide plus date palm fruits in rats after 4 weeks dosing

Experimental groups	Mean±SD	
	Weight at day 0 (g)	Weight after week 4 (g)
Group 1 (control normal saline)	186.75±8.99	199.25±8.02
Group 2 (only DPF)	141.5±14.53	115.75*±11.24
Group 3 (50 mg/kg HCT + DPF)	204.00±16.17	222.00±8.16
Group 4 (25 mg/kg HCT + DPF)	188.5±55.12	163.25#±55.28
Group 5 (50 mg/kg HCT–DPF)	224.5±11.00	200.5#±5.80
Group 6 (100 mg/kg HCT + DPF)	189.00±22.18	155.5*,#±17.71

*Significant difference ($P<0.05$) compared to control; #a significant difference between HCT and DPF plus HCT combination groups. Results represent mean±SD. DPF: Date palm fruit; HCT: Hydrochlorothiazide; SD: Standard deviation

Lipid profile levels among experimental animals after 4 weeks of dosing

Table 2 represents lipid profile determination in all the treatment groups. The results indicate that the HCT only group had a higher level of cholesterol compared to the control significantly ($P < 0.05$). The DPF only group produced a highly significant ($P < 0.05$) reduced cholesterol levels compared to both the control and HCT only treated groups. In addition, all HCT plus DPF treatments showed significantly lower cholesterol levels compared to control. However, only 100 mg/kg plus DPF group showed a significant ($P < 0.05$) lower level compared to HCT only. Overall, all the treatment groups of HCT plus DPF had lower cholesterol compared to the HCT only group. The results therefore indicate that DPFs might have contributed to the lowering of cholesterol levels. Similarly, as observed with cholesterol levels, the same trend was observed with triglycerides levels in all the experimental groups, with the exception of 50 mg/kg and 100 mg/kg plus DPFs showed significantly decreased triglyceride levels compared to the HCT only treated group. Furthermore, LDL levels in the HCT only group showed significantly decreased levels compared to the control. Only 25 mg/kg plus DPF and 100 mg/kg plus DPF groups showed a significantly different level ($P < 0.05$) compared to the HCT only group.

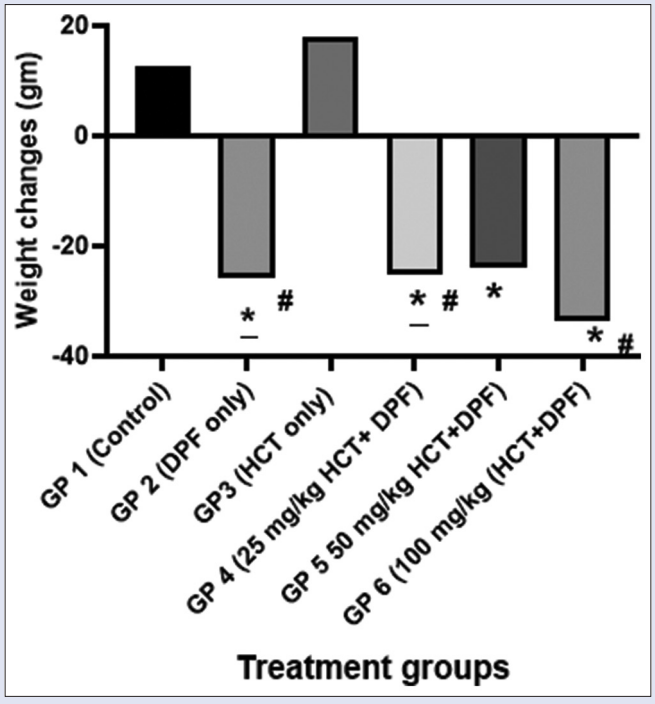

Figure 1: Changes in weight of experimental rats after 4 weeks of dosing with hydrochlorothiazide and hydrochlorothiazide plus date palm fruits. Results represent mean ± standard deviation. *A significant difference ($P < 0.05$) compared to control; #a significant difference between hydrochlorothiazide and date palm fruits plus hydrochlorothiazide combination groups. Date palm fruits, hydrochlorothiazide

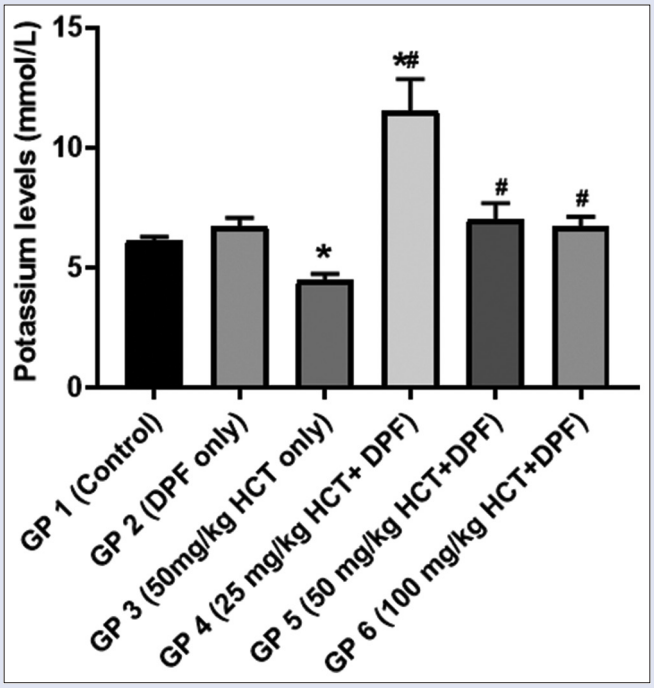

Figure 2: Changes in serum potassium levels in experimental rats after 4 weeks of dosing with hydrochlorothiazide and hydrochlorothiazide plus date palm fruits. Results represent mean ± standard deviation. *A significant difference ($P < 0.05$) compared to control; #a significant difference between hydrochlorothiazide and date palm fruits plus hydrochlorothiazide combination groups. Date palm fruits, hydrochlorothiazide

Table 2: Effect of hydrochlorothiazide and hydrochlorothiazide plus date palm fruits in rats after 4 weeks dosing on lipid profile

Treatment groups	Cholesterol (mmol/L)	Triglycerides (mmol/L)	LDL (mmol/L)
Group 1 (control, normal saline)	2.14±0.09	0.96±0.021	0.21±0.036
Group 2 (DPF)	1.46±0.17*,#	0.88±0.052#	0.2±0.036
Group 3 (50 mg/kg HCT only)	2.27±0.10	1.25±0.05*	0.31±0.015*
Group 4 (25 mg/kg HCT + DPF)	2.10±0.05*	1.44±0.181*	0.24±0.036#
Group 5 (50 mg/kg HCT + DPF)	2.11±0.035*	0.71±0.025*,#	0.30±0.04*
Group 6 (100 mg/kg HCT + DPF)	1.74±0.081*,#	0.65±0.036*,#	0.22±0.017*,#

*Significant difference (P<0.05) compared to control; #a significant difference between HCT and DPF plus HCT combination groups. Results represent mean±SD. DPF: Date palm fruit; HCT: Hydrochlorothiazide; SD: Standard deviation; LDL: Low-density lipoprotein

DISCUSSION

Hypertension is one of the common chronic diseases encountered in Saudi Arabia considered to be the leading risk factor for death.[15,20,21] The use of HCT has spanned five decades and is recommended as a first-line treatment in hypertension due to its significant reduction of stroke and heart attacks associated with hypertension.[22] However, evidence shows that chronic HCT therapy causes hypokalemia among other dose-related adverse effects.[23] Diuretic-induced hypokalemia is of particular concern because the incidence of sudden death in hypertensive subjects treated with the thiazide diuretic HCT is greater than that in matched control subjects.[24] Reports are abound that have showed hypokalemia as a possible underlying cause of life-threatening arrhythmias seen with thiazide therapy.[24] Low serum potassium could predispose at-risk patients, such as those with ischemic heart disease, to ventricular arrhythmias. Hypokalemia due to thiazide diuretics has been implicated as one of the possible causes of reduced insulin secretion and glucose intolerance.[25] Therefore, patients who are on diuretic therapy get potassium supplement. Some of the treatment guidelines suggested include the use of amiodarone and potassium chloride (KCl) supplementation.[24,26] However, the use of such supplements like KCl has been reported to experience gastrointestinal discomfort.[27,28] According to Sinar *et al.*,[27] gastrointestinal distress has been documented with KCl supplementation but not with dietary potassium. Our present study evaluated the concurrent use of DPFs and HCT on animals' weights, serum potassium, and lipid profile. DPFs have been documented to be rich in potassium.[14] Natural products like DPFs have gained increased interest among several investigators, including physicians due to their cancer-protective effects, antioxidant activity, and cholesterol-lowering properties.[29] Hypokalemia is one of the most common electrolyte anomalies usually encountered by physicians in their practice and seen in 40% of outpatients treated with thiazide diuretics.[30,31] To reduce the risk of hypokalemia, studies have suggested the use of dietary potassium supplements, which is implicated in hypertension reduction as well.[32,33] According to Barri and Wingo,[34] 1 g/d dietary potassium intake was shown to lower level of systolic blood pressure by 0.9 mmHg. Therefore, since the average potassium concentration in 100 g of DPFs is 656 mg,[15] potassium supplementation with date palm fruits can deliver the needed amount of potassium, particularly in the presence of hypokalemia due to HCT.

Our finding revealed negative and significant weight changes in rats treated with DPFs only and dates plus HCT. The results suggest that DPFs were contributory to the observed negative weight balance in this study. These were clearly demonstrated in the experimental groups 2, 4, and 6 compared with HCT treatment group 3. This result is consistent with the work of Khezerloo *et al.*[35] who also documented significant weight loss with DPF extract. The report from our study also confirmed that HCT does indeed reduce serum potassium, which was significant compared to control, and it is consistent with the characteristic profile of HCT. Furthermore, we observed restoration of serum potassium levels to almost normal levels with concurrent use of DPFs with HCT. However, we observed that the lowest dose 25 mg/kg produced the highest potassium level and we could not explain these results. Nevertheless, it does appear to be dose dependent, with 100 mg/kg having the lowest increase. Our current observation corroborates our previous study on rabbits,[18] where we reported elevated serum potassium with DPFs. The implication of this preliminary study is that potassium supplementation as earlier reported by Shaikh *et al.*[26] ameliorated hypokalemia. Therefore, it follows that since serum potassium levels were raised by DPFs, a veritable source potassium, dietary supplementation with HCT, might provide benefit and abolish thiazide-induced hypokalemia. The kidney is chiefly responsible for maintaining total body potassium homeostasis; hence, the most common cause of hypokalemia is associated with renal potassium loss.[36] Related studies have reported that appropriate serum potassium levels are definitely required to maintain myocardial function.[37] Potassium, therefore, plays a critical role in many physiological functional activities including insulin release. In particular, thiazide-induced loss of potassium is associated with increased renin–aldosterone system activity which enhances sodium and water delivery to the distal tubule and subsequently potassium excretion. This means that negative serum potassium level is inversely related to plasma renin activity.[38] Our study also revealed that concurrent administration of date palm fruits with HCT decreased the lipid profile among experimental animals. According to Nie *et al.*,[39] hyperlipidemia can be characterized by an elevation of serum total cholesterol, triglyceride, and LDL-C levels. Given the fact that hypertensive patients have a high prevalence of abnormally elevated lipid profile,[40] attenuation of by DPF supplementation could potentially provide a natural alternative. Hence, we observed, in this study, significantly reduced levels of total cholesterol, triglyceride, and LDL-C levels in the DPF only and all combination groups with HCT. Our results were similar to the findings of Nie *et al.*[40] and Bouhlali *et al.*[41] who reported methanolic extracts of date palm fruits exhibited lipid-lowering activity. This finding is also an important observation in that documented evidence reveals that thiazides increase total cholesterol and triglycerides.[22]

CONCLUSION

We have demonstrated in this present study that concurrent administration of DPFs with HCT normalized serum potassium levels in rats, thereby mitigating HCT-induced hypokalemia. In addition, co-administration of HCT with DPFs reduced serum levels of total cholesterol, triglyceride and LDL-C, indicating a potential lipid-lowering activity by DPFs. Therefore, concurrent use of DPFs with HCT could potentially be of interest, since HCT-induced hypokalemia treated with KCl is prone to adverse effects. However, further studies with human subjects are required to elucidate the potential clinical significance of this finding.

Institutional review board statement

The study was conducted according to the guidelines of the Deanship of Scientific Research and approved by the Institutional Ethics Committee of King Faisal University (protocol code KFU-REC/2021-06-09 and February 06, 2021.

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Conflicts of interest

There are no conflicts of interest.

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