

Adipose Tissue Levels of DDT as Risk Factor for Obesity and Type 2 Diabetes Mellitus

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Abstract

Background: Exposure to dichlorodiphenyltrichloroethane (DDT), a potent lipophilic organochlorine pesticide, has long been linked as a risk factor for type 2 diabetes mellitus (T2DM). However, its presence in the adipose tissues of the T2DM subjects has not been explored in the Indian population, where this long-banned pesticide is still in use. The present study was conducted to evaluate the possible association of DDT and its metabolites in obese and non-obese T2DM subjects. **Methods:** Subjects with normal glucose tolerance (n = 50) and T2DM (n = 50) were divided into equal numbers in obese and non-obese groups. Their plasma glucose levels, HbA_{1c}, and lipid profile were measured. The adipose tissues were collected intraoperatively, and DDT and its metabolites were measured using a gas chromatograph equipped with an electron capture detector. **Results:** Obese subjects, irrespective of their glycemic status, and T2DM subjects had higher concentrations of DDT. p, p' DDT was found to increase the odds for diabetes, and o, p' DDT for central obesity. p, p' DDD was also strongly correlated with central obesity, glycemic parameters, and triglycerides. **Conclusion:** The excess deposition of p, p' DDD, o, p' DDT, and p, p' DDT in obese subjects may proceed to T2DM by disrupting triglycerides and glycemic parameters.

Keywords: Adipose tissue, central obesity, DDD, DDT, T2DM

INTRODUCTION

Dichlorodiphenyltrichloroethane (DDT), one of the chemicals listed under dirty dozen persistent organic pollutants,^[1] is a widely known organochlorine pesticide.^[2] The uncontrolled use of DDT has raised many environmental and human health concerns.^[3] DDT is considered ubiquitous, and it has been accepted that every living being on Earth might have a DDT body burden, mainly stored in body fat.^[4] Exposure to DDT and its metabolites are primarily through dietary routes.^[5] DDT transportation out of the gut takes place via the triglyceride component of chylomicrons, which are accountable for their movement from the intestine to adipose tissue, bypassing the liver metabolism.^[6] A substantially more significant body of literature has solidified the obesogenic^[7,8] and endocrine-disrupting properties of DDT and its metabolites.^[9,10] Exposure to such pesticides has been associated with an increasing prevalence of type 2 diabetes mellitus (T2DM).^[11] As T2DM is a chronic disease that develops over time, the evidence of the role of DDT in T2DM from *in vivo* studies is uniform. Interestingly, the possibility

of excess accumulation of these pesticides in subjects with T2DM also exists.^[12]

Adipose tissue plays a dual role by acting as a reservoir for pesticide accumulation and promoting an influential role in the pathogenesis of T2DM.^[13] Some studies reported that pollutants accumulated in adipose tissue might play a more explanatory role in T2DM pathogenesis than adipose tissue itself^[14,15]; hence, we planned this study to estimate the potential association of DDT and its metabolites with obesity parameters subjects with T2DM.

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METHODS

The study was a cross-sectional case-control study conducted from January 2016 to January 2020 at the University College of Medical Sciences and GTB Hospital (University of Delhi), Dilshad Garden, Delhi, India, in which the subjects were recruited prospectively. The study was approved by the Institutional Ethics Committee for Human Research, UCMS, and GTB Hospital, Delhi, India.

Study participants and sample collection

A flow chart has been presented for the study design. Post-hoc statistical power analysis for the study sample size was performed with an alpha of 0.05. The sample size of 50 in each group was projected and needed for the comparison between/within the group. The proposed sample size of 50 per group came to be more than adequate for the study with the power of the study of 80% and for subgroups analysis.

Subjects visiting the hospital for their elective abdominal surgeries were screened, and those fulfilling the inclusion-exclusion criteria were recruited consecutively during the study period. A total of 50 normal glucose tolerance (NGT) subjects, characterized based on oral glucose tolerance test, were matched for age, sex, and BMI with 50 known T2DM subjects and were recruited for the study. These two groups were further categorized into four groups as per their BMI.^[16] Group 1 included 25 NGT subjects with BMI ≤ 22.9 , and group 2 had 25 NGT subjects with BMI ≥ 23 , Group 3 comprised 25 T2DM subjects with BMI ≤ 22.9 , and 25 T2DM subjects with BMI ≥ 23 were included in Group 4. Group 1 was matched with Group 3, and Group 2 was compared with Group 4 concerning their BMI. The T2DM and NGT subjects in these groups were selected based on clinical guidelines provided by the ADA.^[17] Subjects with known hypothyroidism, pancreatic disease, Cushing syndrome, and females with the known polycystic ovarian disease were excluded from the study. Patients with a history of chronic smoking and drinking were also excluded. Before initiating the study, informed consent was obtained from all the included subjects.

Sample collection and clinical measurements

Intraoperatively, adipose tissue samples weighing ~5 g were collected in a sterile container and cryopreserved in liquid nitrogen, followed by their storage at -80°C to estimate OCPs. Venous blood samples were collected, and serum was separated to estimate fasting and postprandial plasma glucose and lipid profile parameters (triglycerides, cholesterol, and high-density lipoproteins). HbA_{1c} was estimated in whole blood.

A detailed proforma was used to record the baseline characteristics of the recruited subjects. Details, including age, gender, BMI (weight (kg)/height (m²)), waist circumference, and blood pressure, were documented. Fasting and postprandial plasma glucose were estimated by oxidase/peroxidase method using Randox UK kit. HbA_{1c} was quantified by HPLC (Bio-Rad analyzer) method.

Pesticides estimation

Extraction and clean-up of pesticide residues

The pesticide extraction for each sample was done in triplicates by Bush *et al.*^[18] method. One gram of chopped tissue was agitated with 1:2 parts of acetone (Merck) and n-hexane (Merck) on a mechanical shaker for 4–5 hours. The solvent was collected, and the procedure was repeated twice. Collected organic phases were combined and clean-up was done by adsorption column chromatography using heat-activated florisil (SRL) and anhydrous sodium sulfate (SRL), and n-hexane as eluent. The eluted solvent was evaporated and reconstituted in 1 mL of n-hexane.

Estimation and confirmation of pesticide residues

The high purity standard of the mixture of DDT and metabolites was obtained from Sigma-Aldrich, USA, and used to calibrate and quantify pesticide residues in samples. Estimation of pesticide residues was undertaken using a gas chromatograph (GC) equipped with an electron capture detector (Perkin Elmer Clarus 500). The Elite GC DB-5 column having a length of 60 m and a diameter of 0.25 mm was used in GC. The oven temperature of GC was programmed for an initial temperature of 170°C with a holding time of 1 min and gradually raised to 225°C at the rate of $5^{\circ}\text{C}/\text{min}$ with a holding time of 5 min and then finally raised to 275°C at the rate of $6^{\circ}\text{C}/\text{min}$ with a holding time of 15 min. The concentration of pesticide residues was quantified by comparing the particular compounds' peak area and retention time in the tissue sample extract to that of the corresponding standard run separately under the same operating conditions. The limit of detection was 1 ppb. The methods' accuracy was confirmed by calculating the recovery from spiked samples with known concentrations of the standards. The mean recovery values ranged from 91.3% to 95%.

Statistical analysis

A post-hoc power of analysis was performed for the sample size calculation. The data were presented as mean \pm standard deviation. Mann–Whitney test was used for nonparametric data analysis. Normally distributed data were compared by one-way ANOVA followed by Tukey's test. Spearman's correlation was used for defining the correlation between pesticides and biochemical parameters. $P \leq 0.05$ was considered statistically significant. All the statistics were done using SPSS 16.0.

RESULTS

Clinical characteristics

The clinical and biochemical parameters of all the study groups are shown in Table 1. All of the T2DM subjects were on metformin, and additional secondary drugs of vildagliptin or glimepiride were administered to control the blood glucose levels, wherever required. None of the patients was on insulin. The participants in each group were matched for their age, gender, and BMI. The mean age of the entire study population was 44.49 ± 8.60 years, and the male/female ratio was comparable in all four groups. As the study subgroups were

Table 1: Clinical and biochemical parameters and their comparisons between the study groups

Parameters	Group 1 (n=25)	Group 2 (n=25)	Group 3 (n=25)	Group 4 (n=25)	P
Age (years)	43.84±8.16	44.12±9.80	45.08±6.85	44.92±9.60	1 vs 2=0.91, 1 vs 3=0.56, 1 vs 4=0.67, 2 vs 3=0.69, 2 vs 4=0.77, 3 vs 4=0.95
Male/Female (n)	9/16	6/19	11/14	7/18	1 vs 2=0.67, 1 vs 3=0.15, 1 vs 4=0.24, 2 vs 3=0.71, 2 vs 4=0.62, 3 vs 4=0.58
BMI (kg/m ²)	21.35±1.02	27.58±2.80	22.06±0.63	27.86±3.60	1 vs 2=0.00, 1 vs 3=0.71, 1 vs 4=0.000, 2 vs 3=0.000, 2 vs 4=0.98, 3 vs 4=0.00
Waist circumference (cm)	85.24±7.99	91.00±7.79	92.64±8.65	101.84±8.83	1 vs 2=0.08, 1 vs 3=0.01, 1 vs 4=0.00, 2 vs 3=0.89, 2 vs 4=0.00, 3 vs 4=0.00
BP systolic (mmHg)	123.64±9.01	123.56±6.67	125.96±11.86	127.68±11.06	1 vs 2=1.00, 1 vs 3=0.84, 1 vs 4=0.47, 2 vs 3=0.83, 2 vs 4=0.46, 3 vs 4=0.93
BP diastolic (mmHg)	79.84±5.40	81.80±6.68	80.24±6.58	82.48±6.20	1 vs 2=0.68, 1 vs 3=0.99, 1 vs 4=0.44, 2 vs 3=0.81, 2 vs 4=0.98, 3 vs 4=0.058
Fasting plasma glucose (mg/dL)	77.84±7.63	82.44±8.66	183.16±40.71	180.12±40.49	1 vs 2=0.95, 1 vs 3=0.00, 1 vs 4=0.00, 2 vs 3=0.00, 2 vs 4=0.00, 3 vs 4=0.98
Post prandial plasma glucose (mg/dL)	119.00±12.39	113.80±14.49	236.68±21.61	236.00±26.97	1 vs 2=0.79, 1 vs 3=0.00, 1 vs 4=0.00, 2 vs 3=0.00, 2 vs 4=0.00, 3 vs 4=0.99
HbA _{1c}	5.21±0.62	5.04±0.37	6.82±1.37	7.50±1.25	1 vs 2=0.93, 1 vs 3=0.00, 1 vs 4=0.00, 2 vs 3=0.00, 2 vs 4=0.00, 3 vs 4=0.09
Triglyceride (mg/dL)	123.64±45.78	122.57±53.04	167.48±65.65	192.28±8.05	1 vs 2=1.00, 1 vs 3=0.07, 1 vs 4=0.00, 2 vs 3=0.07, 2 vs 4=0.00, 3 vs 4=0.49
Cholesterol (mg/dL)	167.72±38.54	181.23±66.01	172.96±36.96	212.52±50.31	1 vs 2=0.77, 1 vs 3=0.98, 1 vs 4=0.01, 2 vs 3=0.93, 2 vs 4=0.12, 3 vs 4=0.03
HDL (mg/dL)	48.44±18.99	44.03±10.76	42.74±13.77	43.93±10.21	1 vs 2=0.68, 1 vs 3=0.47, 1 vs 4=0.66, 2 vs 3=0.99, 2 vs 4=1.00, 3 vs 4=0.99

Data presented as mean±standard deviation. Group 1- NGT, BMI ≤22.9, Group 2- NGT, BMI ≥23, Group 3- T2DM, BMI ≤22.9, Group 4- T2DM, BMI ≥23

categorized based on their BMI, significant differences were observed among the obese and non-obese groups in terms of BMI; their waist circumference also followed the same trend. As expected, glycaemic parameters were significantly higher in Group 3 and Group 4 as compared to Group 1 and Group 2. Fasting triglycerides and cholesterol were also on the higher side in Groups 3 and 4 as compared to other groups, whereas no significant differences in HDL levels were observed among groups.

Adipose tissue levels of DDT and metabolites in study groups

The adipose tissue of all study subjects showed the presence of o, p' DDE, p, p' DDE, p, p' DDD, o, p' DDT, and p, p' DDT. The concentration levels of all of these compounds were found to increase in parallel with respect to the grade of obesity (i.e. Group 1 vs. Group 2, and Group 3 vs. Group 4). The levels of o, p' DDE, p, p' DDD, and o, p' DDT were dominant in the obese diabetic subjects. However, p, p' DDD, o, p' DDT, and p, p' DDT levels were significantly higher in obese T2DM subjects as compared to NGT subjects. No significant differences in o, p' DDE and p, p' DDE levels were observed among the four groups [Table 2]. The levels of p, p' DDD, o, p' DDT, and p, p' DDT were found to be in concordance with the serum triglycerides.

The correlation analysis among all the subjects revealed positive association of adipose tissue levels of p, p' DDD with waist circumference ($r = 0.22$, $P = 0.03$), fasting ($r = 0.37$, $P = 0.00$) and postprandial plasma glucose ($r = 0.36$, $P = 0.00$), HbA_{1c} ($r = 0.35$, $P = 0.00$), and serum

triglycerides ($r = 0.28$, $P = 0.01$) levels. In addition, p, p' DDT was also correlated with all of the glycaemic markers, i.e. fasting ($r = 0.28$, $P = 0.01$), and postprandial plasma glucose ($r = 0.23$, $P = 0.02$), and HbA_{1c} ($r = 0.27$, $P = 0.01$).

DDT and metabolites and risk of obesity

By comparing the DDT and its metabolites levels between the obese and non-obese groups, irrespective of their glycaemic status, we found that all the DDT metabolites had higher concentrations in adipose tissues of the obese subjects. However, only o, p' DDT levels were significantly higher in the obese group as compared to the non-obese group [Table 3].

The correlation of p, p' DDD with fasting plasma glucose ($r = 0.32$, $P = 0.03$), postprandial plasma glucose ($r = 0.35$, $P = 0.01$), HbA_{1c} ($r = 0.34$, $P = 0.02$) and serum triglycerides ($r = 0.36$, $P = 0.01$) was also found in the obese group but the same did not exist among non-obese subjects. Similarly, p, p' DDT correlated significantly with fasting plasma glucose, postprandial plasma glucose, and HbA_{1c} in the obese group but not in the non-obese group as shown in Figure 1. We also found the positive correlation of o, p' DDT with postprandial plasma glucose ($r = 0.31$, $P = 0.03$) and HbA_{1c} ($r = 0.32$, $P = 0.02$). The o, p' DDT was also positively associated with the risk of obesity as shown by the logistic regression model adjusted with other confounding factors such as waist circumference, fasting and postprandial plasma glucose, HbA_{1c}, triglycerides, cholesterol, and HDL [Table 4]. The study group's age, gender, and BMI did not show a correlation with any of the DDT metabolites; therefore, the parameters were not used in the logistic regression analysis.

Table 2: DDT and its metabolites levels (ppb) in the study groups

DDT and metabolites (ppb)	Group 1 (n=25)	Group 2 (n=25)	Group 3 (n=25)	Group 4 (n=25)	P
o, p' DDE	0.57±1.46	1.60±3.21	1.63±5.64	3.23±9.26	1 vs 2=0.12, 1 vs 3=0.49, 1 vs 4=0.62, 2 vs 3=0.06, 2 vs 4=0.35, 3 vs 4=0.27
p, p' DDE	0.86±3.35	2.06±0.90	0.91±3.26	1.61±6.82	1 vs 2=0.31, 1 vs 3=0.59, 1 vs 4=0.59, 2 vs 3=0.16, 2 vs 4=0.17, 3 vs 4=0.97
p, p' DDD	1.51±2.81	2.14±3.51	3.31±2.56	3.87±4.44	1 vs 2=0.76, 1 vs 3=0.001, 1 vs 4=0.001, 2 vs 3=0.007, 2 vs 4=0.004, 3 vs 4=0.81
o, p' DDT	1.07±1.58	1.49±1.95	1.16±1.63	3.42±3.69	1 vs 2=0.46, 1 vs 3=0.56, 1 vs 4=0.005, 2 vs 3=0.89, 2 vs 4=0.04, 3 vs 4=0.03
p, p' DDT	1.21±0.87	1.15±1.02	2.04±1.81	2.45±1.99	1 vs 2=0.60, 1 vs 3=0.18, 1 vs 4=0.04, 2 vs 3=0.07, 2 vs 4=0.014, 3 vs 4=0.44

Data presented as mean±standard deviation. Group 1- NGT, BMI <22.9, Group 2- NGT, BMI ≥23, Group 3- T2DM, BMI <22.9, Group 4- T2DM, BMI ≥23

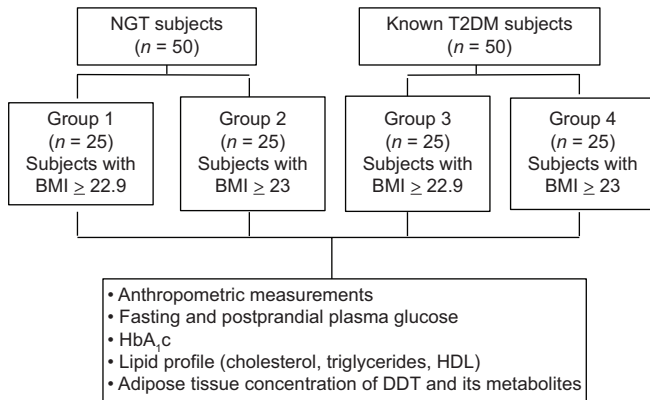


Figure 1: Study design

DDT and metabolites and risk of T2DM

Similarly, comparing these parameters between T2DM and NGT groups, p, p' DDD, o, p' DDT, and p, p' DDT levels were significantly higher in T2DM subjects. The levels of o, p' DDE and p, p' DDE were also higher in the T2DM group than in the NGT group but were not found statistically significant [Table 5]. The correlation analysis in the T2DM group among the parameters did not signify conclusive findings as none of the DDT metabolites was associated with any of the risk factors for T2DM. However, the logistic regression analysis among all the study subjects, adjusted for waist circumference, triglycerides, and HDL, revealed that p, p' DDT was strongly associated with the risk of T2DM [Table 4].

DISCUSSION

In the current study, we investigated whether DDT and its metabolites accumulated more in adipose tissue of obese and T2DM subjects and whether these shared any association with waist circumference and lipid profile parameters. The results suggest high levels of DDT and metabolites in adipose tissues of subjects with obesity and T2DM and even higher in obese subjects with T2DM. There is an increased risk of developing obesity with o, p' DDT accumulation; however, p, p' DDT was strongly associated with the risk of occurrence of T2DM. Interestingly, p, p' DDD, p, p' DDT, and o, p' DDT levels were in concordance with the triglycerides levels in the

Table 3: DDT and its metabolites levels (ppb) comparison between obese and non-obese subjects

DDT and metabolites (ppb)	Non-obese (n=50) (Mean±SD)	Obese (n=50) (Mean±SD)	P
o, p' DDE	1.10±4.11	2.42±6.91	0.06
p, p' DDE	0.88±3.27	1.82±6.78	0.48
p, p' DDD	2.39±2.81	3.00±4.06	0.75
o, p' DDT	1.12±1.59	2.48±3.09	0.03
p, p' DDT	1.62±1.47	1.80±1.69	0.86

obese diabetic group, suggesting that these pesticides in body fats may alter lipid metabolism as well.

The present study revealed the possible mechanism of toxicity posed by these pesticides; however, there were certain limitations. First, the possibility of a cause-effect relationship could not be implied by these findings due to the stringent inclusion and exclusion criteria in selecting the subjects and exploring the pesticides levels in abdominal adipose tissue; the study's sample size was small.

In this study, we recruited an equal number of obese and non-obese NGT and T2DM subjects. Though their BMI and waist circumference differed significantly between obese and non-obese groups, waist circumference between non-obese NGT and non-obese T2DM, and obese NGT and obese T2DM also showed a significant difference, suggesting the central obesity to be prominent among T2DM subjects, and supports the waist circumference to be a better obesity-related predictor of T2DM than BMI.^[19]

The growing body of epidemiological studies has raised concern for the obesogenic effects of DDT. Several prospective cohort studies have identified the positive association of DDT/DDE with obesity and/or being overweight^[20-23] Our findings were consistent with these speculations as higher concentrations of DDT and metabolites were found in the respective obese groups of both NGT and T2DM subjects, though the levels were not statistically significant, which might be explained by the smaller number of study subjects per group. The pesticides accumulation was there in a more considerable amount in obese subjects. Though we did not

Table 4: Odds ratio for obesity and T2DM

DDT and metabolites (ppb)	Obesity			T2DM		
	Adjusted* odds ratio	95% CI	P	Adjusted# odds ratio	95% CI	P
o, p' DDE	1.037	0.908-1.184	0.589	1.019	0.876-1.186	0.808
p, p' DDE	1.056	0.937-1.192	0.372	0.990	0.859-1.140	0.885
p, p' DDD	1.070	0.904-1.267	0.431	1.124	0.947-1.334	0.180
o, p' DDT	1.354	1.022-1.794	0.035	1.205	0.903-1.607	0.205
p, p' DDT	1.025	0.722-1.454	0.891	1.844	1.114-3.052	0.017

*Adjusted for waist circumference, fasting plasma glucose, postprandial plasma glucose, HbA1c, triglycerides, cholesterol, and HDL. #Adjusted for waist circumference, triglycerides, and HDL. CI - confidence interval

Table 5: DDT and its metabolites levels (ppb) comparison between T2DM and NGT subjects

DDT and metabolites (ppb)	NGT (n=50) (Mean±SD)	T2DM (n=50) (Mean±SD)	P
o, p' DDE	1.08±2.53	2.43±7.63	0.24
p, p' DDE	1.26±5.29	1.42±5.30	0.17
p, p' DDD	1.83±3.16	3.59±3.61	0.00
o, p' DDT	1.28±1.76	2.29±3.05	0.05
p, p' DDT	1.18±0.94	2.24±1.89	0.00

find any correlation of DDT and its metabolites with BMI, p, p' DDD was strongly associated with waist circumference. The OR of obesity was statistically associated with o, p' DDT. The results were well supported by previous findings of a positive association of o, p' DDT and p, p' DDT with waist circumference and BMI.^[24,25]

The adipose tissues of T2DM subjects had higher concentrations of all of the DDT metabolites, though only p, p' DDD, o, p' DDT, and p, p' DDT were there in significantly higher levels. The association of DDT and its metabolites with reduced insulin sensitivity and glucose metabolic dysregulation has been supported by *in vivo* and *in vitro* studies.^[26] Our results were consistent with these findings as we also observed a positive correlation of p, p' DDD, o, p' DDT, and p, p' DDT with all the glycemic markers. There is a scarcity of evidence in the existing literature regarding the potential role of DDD as it has not been evaluated to that extent. To the best of our knowledge, this is the first study to report the pathogenic association of p, p' DDD with glucose intolerance that suggests the tissue-specific presence and toxic kinetics of this DDT metabolite.

Chronic exposure of p, p' DDT to pancreatic β cells has been found to result in reduced protein expression of genes associated with hyperglycemic stress response.^[27] Indeed p, p' DDT increased the odds of T2DM significantly. However, we failed to establish p, p' DDD exposure as the risk factor for T2DM as it modestly increased the odds of T2DM.

The adipose tissue can display distinctive structural properties and features that may ultimately influence the toxicant's kinetics deposited there.^[28] *In vivo* studies on humans and rodents have reported the adverse effects of DDT and DDE

on lipid homeostasis associated with obesity, and a disruptive endocrine mechanism has been implicated for these disruptive metabolic outcomes.^[29,30] Our results from correlation statistics signified the positive association of serum triglycerides and central obesity with the adipose tissue levels of p, p' DDD, which put forward the possible mechanism of deposition of these lipophilic pesticides in obese subjects. The study outcomes suggest that p, p' DDD may disarray the circulating TGs, and along with o, p' DDT and p, p' DDT, they may derange glycemic parameters as well, which may chronically enhance the risk of T2DM or promote the pathogenesis for the same in obese subjects.

Further research on a larger population could help better understand the mechanism of action of DDT in adipose tissue and its potential role in T2DM. The cellular and molecular level changes in adipocytes due to these pollutants deposition may establish the actual causal relationship.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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