Original Article

Retinoic Acid Receptor Responder Protein 2 and Intelectin-1 in Visceral Adipose Tissue from Pregnant Women with Gestational Diabetes Mellitus

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ABSTRACT

Introduction: The adipose tissue secretes chemerin and omentin related to metabolic diseases. It has been reported that both proteins encoded by retinoic acid receptor responder protein 2 *(RARRES2)* and intelectin-1 *(ITLN1)* genes, respectively, are abnormally expressed in gestational diabetes mellitus (GDM). **Aim:** To evaluate the expression of these genes in visceral adipose tissue in pregnant women with GDM. **Methods:** Descriptive cross-sectional study, with two groups, (A) GDM and (B) control group (pregnant women without GDM). Body mass index (BMI), blood pressure, lipids, and glucose were measured. *RARRES2* and *ITLN1* mRNA expression were evaluated using quantitative real-time Reverse transcription-polymerase chain reaction using TaqMan probes. Statistical analysis was performed using Kolmogórov–Smirnov, Pearson-Spearman correlation, Kruskal–Wallis tests, and *R* language with Shapiro–Wilk, SPSS V21.0. **Results:** Sixty-six women were included. Women with normal weight were more frequent in the control group (33.3%) than GDM (15.2%); overweight was similar in both groups (45.5%), and obesity was less common in the control group (21.2%) than GDM (39.3%). No differential expression of *RARRES2* and *ITLN1* genes among cases and controls were found, but *RARRES2* expression differed ($P = 0.016$) between normal-weight and overweight women in the control group, and *ITLN1* expression significantly differed ($P = 0.002$) between overweight and obese women in the GDM group. **Conclusions:** *ITLN1* could have a role in the GDM severity based on the BMI of the patients.

KEYWORDS: *Body mass index, gestational diabetes mellitus, hyperglycemia, intelectin-1, obesity, overweight, pregnancy, retinoic acid receptor responder protein 2*

INTRODUCTION

*G*estational diabetes mellitus (GDM), defined as carbohydrate intolerance, is one of the most common obstetric complications and is attributed to insulin resistance (insufficient insulin production) caused by reduced pancreatic β-cell function.[1,2] The International Diabetes Federation estimates that GDM occurs in approximately 14% of pregnancies worldwide,[3] showing a wide range of prevalence (1%–20%).[4] GDM etiology is multifactorial caused by an interaction of environmental, epigenetic, genetic, and intrinsic factors.[5]

Major risk factors for GDM include: Maternal maternal overweight and obesity, Type 2 diabetes mellitus (T2DM), in addition to atherosclerosis, dyslipidemia, hypertension, vascular dysfunction and other cardiovascular parameters,[6] as well as neonatal

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complications such as injuries at birth, macrosomia, prematurity, shoulder dystocia, and metabolic alterations in the mother and offspring.[7]

The genetic risk factor associated with GDM development include variants and abnormal expression of genes encoding proteins involved in the insulin signaling, lipid metabolism, among other metabolic processes, leading to complications in the mother and fetus.[8] Due to their participation in cell signaling, adipokines, such as omentin-1 and chemerin, have been suggested as indicators of insulin resistance and have been involved in T2DM and GDM.[9-11] Omentin, encoded by the intelectin-1 (*ITLN1)* gene, is mainly produced and secreted by the visceral adipose tissue (VAT) and is predominantly expressed in VAT stromal vascular cells. Omentin-1 has been shown to be downregulated by insulin and glucose, resulting in reduced levels in metabolic syndrome, obesity, overweight, polycystic ovary syndrome, T2DM, and GDM.[12]

Chemerin, is encoded by the retinoic acid receptor responder protein 2 (*RARRES2)* gene and has been associated with a variety of cardiovascular, inflammatory, and metabolic diseases. This gene is expressed in various human tissues, mainly in the liver, subcutaneous tissues, and VAT, and is correlated with body mass index (BMI) and obesity.[13] Liang *et al.* found that *RARRES2* mRNA expression is 6–24 times higher in visceral and subcutaneous adipose tissue in comparison with the levels detected in the placenta and that the relative mRNA expression and protein levels are markedly increased in both adipose tissue and placental samples of patients with diabetes.[14] The objective of this study was to evaluate the mRNA expression of *RARRES2* and *ITLN1* in the VAT in pregnant women with GDM.

METHODS

Study design

A cross-sectional, descriptive study was conducted at "Mónica Pretelini Sáenz" Maternal Perinatal Hospital (HMPMPS), Health Institute of the State of Mexico, Toluca, Mexico, between August 2018 and December 2019. The study participants were categorized into two groups: (a) Pregnant women with GDM who underwent elective cesarean delivery (GDM group) and (b) pregnant women with a healthy pregnancy (control group). Women with T2DM, twin pregnancies, or BMI ≤ 18.5 kg/m^2 were excluded. Cases with inadequate adipose tissue samples from the cesarean delivery were discarded from the final analysis.

Anthropometry

The BMI of each patient was determined by calculating the weight in kilograms at the beginning of pregnancy and the height in centimeters and using the formula weight/height^2 (kg/m^2). In accordance with international standards (WHO), three BMI categories were considered: Normal weight (BMI: 18.5–24.9 kg/m^2), overweight (BMI: 25–29.9 kg/m^2), and obesity (BMI: ≥ 30 kg/m^2).

Blood pressure (BP) was measured with International organization for standardization (ISO) 2009-approved aneroid sphygmomanometers provided by the hospital in accordance with the recommendations of the Official Mexican Standard (NOM)-030-SSA. BP measurement was performed with the patient at 60°, and the patient's left arm was extended and placed on the support of the stretcher.

Laboratory analyses

Blood samples were obtained to determine the levels of the following biomarkers using the Accu-Chek® equipment: Triglycerides (mg/dL), total cholesterol (mg/dL), high-density lipoprotein cholesterol (mg/dL), low-density lipoprotein cholesterol (mg/dL), and glucose (mg/dL).

Gene expression analysis

The Fatty Tissue RNA Purification Kit (Norgen Biotek Corp. Cat. No. 36200) was used for RNA extraction in accordance with the manufacturer's specifications. RNA was quantified using spectrophotometry (NanoDrop One, Thermo Fisher Scientific), and genetic expression was determined by Reverse transcription-quantitative polymerase chain reaction (qPCR) as follows: First, cDNA was generated from RNA by using the SuperScript II Reverse Transcriptase Kit (Thermo Fisher Scientific, Cat. No. 18064022). Subsequently, qPCR was performed in triplicate for each sample by using the TaqMan probes for *ITLN1* (ThermoFisher Scientific TaqMan assay cat. Hs00914745) and *RARRES2* (Thermo Fisher Scientific TaqMan assay cat. Hs00414615). *GAPDH* was used as an endogenous control for gene expression normalization. To determine the relative expression of the genes in the patients with GDM with respect to that in the controls, the $2^{-\Delta CT}$ method was used, where ΔCT = (problem CTgene-endogenous CTgene). The qPCR data were analyzed with QuantStudio™ Real-Time PCR Software v. 1.3 (Applied Biosystems, Thermo Fisher Scientific, Waltham, Massachusetts, USA).

Ethics

This project was authorized by the Ethics in Research Committee of the HMPMPS (code 2018-05-592), which

is currently registered with the National Bioethics Commission (CONBIOETICA). The procedures in the study were carried out under the ethical considerations recognized by the Declaration of Helsinki (Fortaleza, Brazil) and all patients signed informed consent.

Statistical analysis

Quantitative variables were represented by measures of central tendency. First, the Kolmogorov test was performed to determine the normality of the variables, and the Student's *t*-test or Mann–Whitney *U*-test was used to compare quantitative variables between both groups. Based on the Gaussian distribution of the variables, either Pearson or Spearman correlations were used to evaluate the variables. The Kruskal–Wallis test was used to compare variables in BMI categories.

The gene expression levels were calculated, and statistical analysis was performed using R programming language. Shapiro–Wilk statistical tests were used to determine the normality of the relative expression dataset. To evaluate the expression of both genes, ΔCT was estimated from the difference between the computed tomography (CT) values of the test gene and the CT of the endogenous reference gene. To determine differences in expression levels between the groups, the 2-ΔΔCT test was used. The statistical significance of the data was determined using the nonparametric Mann–Whitney *U*-test. In all cases, $P \leq 0.05$ was considered statistically significant. Statistical analyses were performed using the SPSS program, version 19 (Armonk, New York, USA).

RESULTS

Sixty-six women were included in the study (mean age of 30.31 ± 5.02 years of age), 33 patients with GDM and the same number of patients in the control group. Each group was stratified by BMI, and the following percentages were obtained in the control and GDM groups, respectively: normal weight, 33.3% and 15.2%; overweight, 45.5% and 45.5%; and obesity, 21.2% and 39.4%. The main characteristics of the study population are summarized in Table 1. The two groups showed no differences in terms of maternal and gestational age, schooling, or occupation at the time of pregnancy termination.

GDM detection in the second trimester was higher in the overweight (67.7%) and obesity (66.7%) groups. Women with obesity and GDM had higher weight ($P = 0.034$) and prepregnancy BMI ($P < 0.0001$). Moreover, statistically significant intergroup differences were observed for diastolic BP in patients with obesity (control group, 77.1 ± 11.2 mmHg vs. GDM group, 78.50 ± 11.55 mmHg, $P = 0.04$). In the GDM

group, the highest fasting glucose levels were observed in the overweight (115.41 ± 45.66 mg/dL) and obesity (117.35 ± 20.60 mg/dL, $P = 0.038$) subgroups, and triglyceride levels were also higher in the overweight (292.60 ± 11.67 mg/dL) and obesity (305.25 ± 51.77 mg/dL, $P = 0.008$) subgroups [Table 2].

No differential expression of *RARRES2* and *ITLN1* genes among cases and controls were found, but *RARRES2* expression differed ($P = 0.016$) between normal-weight and overweight women in the control group, and *ITLN1* expression significantly differed ($P = 0.002$) between overweight and obese women in the GDM group. Even more, when the findings for the entire study population ($n = 66$) were considered, *ITLN1* expression was positively correlated with glucose ($r^2 = 0.662$, $P \leq 0.001$) and cholesterol ($r^2 = 0.300$, $P = 0.026$) levels. In the control group, it was observed a positive correlation between *ITLN1* and weight gain ($r^2 = 0.417$, $P = 0.027$), while in the GDM group, *ITLN1* was positively correlated with the triglyceride level ($r^2 = 0.507$, $P = 0.007$) [Table 3].

DISCUSSION

Weight gain and alterations in lipid and glucose profiles play important roles in GDM development. The available data on the significance of circulating chemerin and omentin-1 levels in women with GDM are inconsistent. An analysis of 20 studies, which included 1493 GDM patients and 1488 normal pregnant women, did not show significant differences in circulating chemerin levels which coincide with our results. In that same review, the circulating omentin-1 levels were significantly lower in women with GDM than in healthy controls. These results suggest that omentin-1 has the potential as a novel biomarker for the prediction and early diagnosis of GDM.[10]

An additional review, including ninety-one studies with a total of 11,074 pregnant women, concluded that data regarding several adipokines in GDM are conflicting.[15] In this survey, the lack of significance in the differences in the *ITLN1* and *RARRES2* expression levels in the VAT differs from the findings reported, where patients with GDM showed lower omentin levels than the controls.[16] Mierzyński *et al*. found that the mean concentration of omentin-1 in serum at 24–28 SDG was significantly lower in the DMG group than in the control group,[9] this is related to the fact that the expression levels of these proteins present characteristics of each tissue and stage of pregnancy development in which they are measured. Similarly, Barker *et al*. demonstrated a significant decrease in the maternal circulating omentin-1 concentration in patients with GDM compared to

Table 1: Sociodemographic characteristics of the participants according to the study group according to pre-pregnancy body mass index

Variable	Group							
	Control group			P	Gestational diabetes mellitus			P
	Normal (*n*=11; 33.3), *n* (%)	Overweight (*n*=15; 45.5%), *n* (%)	Obesity (*n*=7; 21.2%), *n* (%)		Normal (*n*=5; 15.2), *n* (%)	Overweight (*n*=15; 45.5%), *n* (%)	Obesity (*n*=13;39.4%), *n* (%)	
Age (mean±SD)	29.3±4.3	31.6±4.9	28.7±4.02	0.294	29.33±4.50	27.93±3.32	33.58±6.18	0.051
Scholarship (%)								
Basic	72.7	46.7	71.4	1.000	60.0	20.0	32.9	1.000
Mean	23.3	20	28.6	1.000	40.0	60.0	50.0	0.411
High	-	33.3	-	1.000	-	20	17.1	0.526
Occupation (%)								
Housewife	90	100	100	0.357	100	100	100	1.000
Professional	10	-	-	0.368	-	-	-	1.000
Marital status (%)								
Married	45.5	33.3	33.3	0.810	60.0	60.0	25.5	0.271
Free union	54.5	66.7	66.7	0.810	40.0	40.0	75.5	0.271
Parity (%)								
First-born	18.2	26.7	-	0.331	60.0	60.0	16.7	0.078
Multigesta	81.8	73.3	100	0.331	40.0	40.0	83.3	0.078
Caesarea diagnosis reason (%)								
Risk of loss of fetal well-being	-	20	42.9	0.567	30	18.2	45.2	1.000
Lack of progression of labor (iterative cesarea)	81.8	53.3	42.9	0.567	40	67.4	19.2	1.000
Breech position	18.2	26.7	14.3	0.567	30	14.4	35.3	1.000
WG (mean±SD)	38.09±0.9	38.6±0.98	38.7±0.95	0.357	38.00±1.45	37.91±1.10	37.91±1.10	0.581
Trimester in which GDM was diagnosed								
1st					-	13.3	16.7	0.518
2nd					60.0	67.7	66.7	
3rd					40.0	20.0	16.7	
Type of treatment								0.846
Insulin					20.0	16.7	8.3	
Insulin+HO					20.0	16.7	16.7	
Diet					60.0	66.7	75.0	

Data are expressed as a (%), mean±SD. WG: Weeks of gestation, GDM: Gestational diabetes mellitus, HO: Oral hypoglycemic, SD: Standard deviation

healthy pregnant patients, as well as an association with maternal obesity during pregnancy.[17]

Omentin-1 has insulin-sensitizing properties and participates in metabolic adaptations in pregnancy by stimulating insulin-mediated glucose uptake in adipocytes. Omentin-1 is synthesized in the adipose tissue and the placenta and serum concentrations are higher in the first trimester of pregnancy and decrease subsequently.[18] Moreover, in patients with GDM, the expression and secretion of omentin-1 are reduced in the adipose tissue and placenta; thus, omentin-1 measurement in the first trimester of pregnancy has been proposed as a predictor of GDM. For example, Abell *et al*. described that between 12 and 15 weeks of pregnancy, an omentin-1 value lower than 38.36 ng/mL is associated with a four-fold higher risk of GDM.[19]

A previous meta-analysis that included 42 eligible studies showed no significant difference in omentin-1 concentration between patients with Type 1 diabetes mellitus and controls. On the other hand, lower concentrations of omentin-1 were observed in patients with GDM or T2DM than in controls, suggesting that omentin-1 concentrations may be an important indicator of GDM and T2DM.[20] As a matter of fact, omentin-1 has been shown to be correlated with GDM development, and decreased serum omentin-1 may lead to insulin resistance, contributing to the pathophysiology of GDM.[16]

In this study, weight gain in the GDM group was associated with an increase in *ITLN1* expression. By contrast, Zhou *et al*. identified lower expression and secretion of the adipokine of this gene (omentin-1) in the

Table 2: Metabolic characteristics of the participants according to the study group according to the prepregnancy body mass index

Variables	Group							
	Control group				GDM			
	Normal (*n*=11; 33.3%)	Sobrepeso (*n*=15; 45.5%)	Obesity (*n*=7; 21.2%)	*P*	Normal (*n*=5; 15.2%)	Overweight (*n*=15; 45.5%)	Obesity (*n*=13; 39.4%)	*P*
Height (m)	1.55±0.06	1.56±0.05	1.54±0.0	0.456	1.58±0.05	1.53±0.5	1.50±0.1	0.210
Pregestational weight (kg	55.5±9.9	67.6±6.3	82.4±16.6	0.000*	58.0±4.8	64.3±7.0	76.0±13.2	0.003*
Gestational weight (kg)	66.9±11.0	75.8±7.8	88.3±20.6	0.048*	70.0±5.6	74.7±8.90	86.6±17.5	0.031*
Increased weight (kg)	−23.2±5.5	−8.2±5.04	−0.35±8.9	0.034*	12.06±5.05	10.3±5.7	10.0±9.5	0.000*
BMI pregestational (kg/m²)	22.9±2.9	27.4±1.5	34.5±5.9	0.000*	22.8±1.0	27.3±1.2	33.4±2.7	0.000*
Systolic blood pressure (mmHg)	118.0±8.3	123.2±6.5	123.7±12.1	0.065	114.8±12.0	120.3±12.5	126.5±13.0	0.157
Diastolic blood pressure (mmHg)	71.8±6.0	75.3±5.1	77.1±11.2	0.048*	72.8±10.5	73.0±9.1	78.5±11.5	0.049*
Glucose (mg/dL)	81.2±9.6	82.8±11.9	94.4±19.3	0.068	89.7±17.6	115.4±45.6	117.3±20.6	0.038
Triglycerides (mg/dL)	197.1±83.4	219.3±63.6	216.2±59.0	0.439	151.5±5.8	292.60±11.67	305.2±51.7	0.008
Cholesterol (mg/dL)	185.0±65.5	196±78.6	209.5±18.2	0.982	186.1±37.2	235.7±82.6	274.0±82.4	0.270
Leukocytes (×10³/µl)	7.2±3.6	7.6±2.3	8.0±2.4	0.990	7.1±0.6	7.5±1.3	8.8±1.7	0.510
Erythrocytes (×10⁶/µl)	4.1±0.8	4.4±0.3	4.5±0.5	0.885	4.6±0.9	4.7±0.2	4.0±0.7	0.370
Hemoglobin (g/dl)	13.5±0.8	13.2±1.1	13.0±2.3	0.861	13.90±0.3	12.70±1.6	12.81±1.1	0.131
Platelets (×10³/µl)	198.0±56.6	203.1±60.2	215.4±46.1	0.795	197.00±54.3	218.91±51.0	261.00±18.4	0.116
Lymphocytes (×10³/µl)	2.15±1.4	0.4±0.09	1.58±0.4	0.660	2.2±0.62	1.0±0.4	0.4±0.6	0.999
Monocytes (×10³/µl)	1.5±1.5	5.6±1.6	0.85±0.7	0.039*	1.2±0.6	1.0±0.1	0.4±0.1	0.181
Granulocytes (×10³/ml)	6.3±2.9	5.9±2.1	5.3±1.4	0.420	4.2±3.2	4.2±2.3	4.1±2.8	1.000

Data are expressed as mean±SD. *P<0.05, NS. Kruskal-Wallis statistical test. BMI: Body mass index, NS: Not significant, SD: Standard deviation, GDM: Gestational diabetes mellitus

Table 3: Spearman's correlation between Omentin-1 (*ITLN1*), Chemerin (*RARRES2*) and metabolic variables

Variable	Control group				GDM			
	Omentin-1 (*ITLN1*) (*n*=28)		Chemerin (*RARRES2*) (*n*=33)		Omentin-1 (*ITLN1*) (*n*=27)		Chemerin (*RARRES2*) (*n*=33)	
	r^2	*P*	r^2	*P*	r^2	*P*	r^2	*P*
Systolic blood pressure (mmHg)	−0.013	0.949	0.344	0.054	−0.150	0.456	0.152	0.405
Diastolic blood pressure (mmHg)	0.115	0.561	0.131	0.476	−0.263	0.185	0.086	0.641
Increased weight (kg)	0.417	0.027*	0.101	0.582	−0.146	0.466	0.110	0.549
Pregestational BMI (kg/m²)	0.285	0.141	0.275	0.128	0.222	0.265	−0.002	0.902
Glucose (mg/dL)	−0.056	0.777	0.040	0.828	−0.082	0.683	0.131	0.476
Cholesterol (mg/dL)	−0.041	0.836	0.022	0.906	0.220	0.269	0.093	0.613
Triglycerides (mg/dL)	0.099	0.615	−0.068	0.712	0.507	0.007*	−0.283	0.116

Statistically significant. *P<0.05, NS. Kruskal-Wallis statistical test. NS: Not significant, BMI: Body mass index

omental adipose tissue of pregnant patients with obesity in comparison with pregnant women with a healthy weight.[21] The difference between our results and other studies can be attributed to differences in the age of the participants, weight, ethnic group, and the duration of pregnancy at the time of sampling.

Glucose and insulin inhibit omentin-1 expression and secretion in adipocytes in a dose-dependent manner.[22] Omentin-1 enhances insulin-stimulated glucose uptake in human adipocytes and has insulin-sensitizing properties, expressing in the heart, lungs, ovary, and placenta.[23] Omentin-1 has been shown to be downregulated by insulin and glucose, resulting in decreased levels in overweight women affected with polycystic ovary syndrome.[24] As stated previously, decreased omentin-1 levels have been found in patients with obesity and diabetes. Franz and Brian also reported that higher omentin-1 concentrations in the fetus may be crucial to enhance a growth-promoting effect.[18] Through univariate logistic regression model, a significant correlation between omentin-1 concentration and preterm birth occurrence has been found.[9]

Chemerin levels are independently associated with endothelial activation and early atherosclerosis in newly diagnosed T2DM.[25] Recent studies have indicated that chemerin is released from adipose tissue, and because serum albumin levels are usually decreased in late pregnancy due to the increasing nutritional needs of the fetus, it may partly explain the lower levels of circulating chemerin in patients with GDM during the third trimester of pregnancy.[26]

Previous studies showed lower serum chemerin levels in patients with GDM in comparison with a control group.[27] As our findings showed that women with normoglycemic obesity had higher levels of chemerin gene (*RARRESS2*) expression than normal-weight pregnant women, a possibility exists that the BMI could be a factor affecting maternal chemerin levels in GDM.[28]

An important issue is that chemerin levels can reduce to values comparable to those in the control group during the dietary restriction,[29] and a correlation between GDM and chemerin levels is biologically plausible. Following this line of research, chemerin has been associated with adipocyte differentiation and lipolysis, and a reduction in chemerin levels may be associated with multiple factors associated with GDM development, including decreased insulin sensitivity, anti-inflammatory capacity, lipometabolism, pregnancy, obesity, diet, and exercise.[24]

Chemerin is credited with a preinflammation function,[30] and chronic low-grade inflammation has been shown to promote insulin resistance. In this survey, there were no data confirming a difference in inflammation, at least in the hematic cytometry. On the other hand, chemerin is positively associated with an increased risk of GDM in early and mid-pregnancy. Chemerin may also be implicated in the GDM pathogenesis, with significant associations detected approximately 10–18 weeks before typical GDM screening.[11]

Tsiotra *et al*. described that *RARRES2* expression was significantly higher in the VAT than in the subcutaneous adipose tissue and its expression in the placenta was negligible in all women. They concluded that *RARRES2* levels are elevated, and *ITLN1* levels are decreased in women with GDM complicated by obesity.[15] This finding, together with the positive association of chemerin with markers of insulin resistance, suggests that these adipokines, especially chemerin, and their adipose tissue expression could contribute to the increased insulin resistance and low-grade inflammation that characterizes obese women with GDM. In our study, *RARRES2* expression differed between normal-weight and overweight women only in the control group

and *ITLN1* expression significantly differed between overweight and obese women only in the GDM group.

This study has some limitations; the sample size in each study group was not sufficiently large to yield convincing results; moreover, longitudinal studies are required to determine adiposity with greater precision and evaluate its impact on the regulation of different metabolic and inflammatory mediators during pregnancy. However, this study provides new information regarding its differential expression depending on the BMI for *RARRES2* in GDM and for *ITLN1* in a healthy pregnancy.

CONCLUSIONS

Our study suggested that *ITLN1* levels could be associated with weight gain in pregnancy only in the control group and with triglyceride levels only in the GDM group, this linked to physiological adaptations of pregnancy and its outcome. However, the mechanisms underlying the effects of these adipokines in the pathogenesis of GDM are unclear and remain to be investigated. Since obesity in pregnancy affects gene expression in VAT. Since the associations analyzed between *ITLN1* and *RARRES2* and the metabolic variables in uncomplicated pregnancy and GDM should be measured from the prepregnancy stage to study the impact of weight change. Therefore, future studies are required to clarify the association between *ITLN1* and *RARRES2* during pregnancy and thus understand the trajectories and associations with GDM risk. So that it can be used as a prenatal prognosis.

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Conflicts of interest

There are no conflicts of interest.

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