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Assessment of the efficacy of omega-3 fatty acids on metabolic and inflammatory parameters in patients with schizophrenia taking clozapine and sodium valproate☆

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ABSTRACT

Omega-3 fatty acid (FA) supplementation has been reported to improve several cardio-metabolic risk factors. We aimed to assess the efficacy of omega-3 fatty acids on metabolic and inflammatory indices in patients with schizophrenia who were taking clozapine and sodium valproate. All patients were on a stable dose of 300–400 mg of clozapine for 3 months. Subjects were randomized to treatment with either omega-3 fatty acid (4 gr/day) or a placebo for 8 weeks. Height, weight, abdominal circumference, serum lipid profile, fasting blood glucose (FBG), and serum high sensitivity-C-reactive protein (hs-CRP) were determined at baseline and after 8 weeks of treatment. Fifty six subjects were recruited into the study. Patients with schizophrenia who were in the group receiving omega-3 FA capsules had an improvement in some anthropometric indices including weight, BMI, wrist and waist circumference, compared to the placebo group. Only changes in waist circumferences remained significantly different after adjustment for serum fasted TG. Our results showed omega-3 FA supplementation can improve some anthropometric indices in patients with schizophrenia who are taking clozapine pharmacotherapy.

1. Introduction

According to the World Health Organization (WHO), schizophrenia is an extreme mental condition affecting more than 21 million individuals globally. People with schizophrenia are 2–2.5 times more likely to die prematurely than other people. This is often because of physical health problems that include: cardiovascular, metabolic and infectious diseases (WHO, 2015). Abnormalities in membrane lipids and redox controlling systems may be a cause of a number of features of schizophrenia, and better treatments to prevent schizophrenia, and its co-morbidities are required (Bentsen et al., 2013; English et al., 2013). Anti-psychotic treatment and poor lifestyle can increase the risk of metabolic problems in schizophrenia. Treatment with n-3 poly unsaturated fatty acids (PUFA) has been reported to reduce the potential metabolic side effects of drug therapy, and enhance the level of functioning in first-episode schizophrenia patients (Pawelczyk et al., 2015a). And there is also evidence that n-3 PUFA may reduce the intensity of adverse impacts associated with antipsychotics. Short-term (6 weeks) n-3 PUFA supplementation can improve cardio-metabolic risk factors in patients treated with olanzapine and either valproate or lithium (Pawelczyk et al., 2015b; Faghihi et al., 2012). Whilst several trials have reported that omega-3 PUFA have beneficial effects in patients with schizophrenia (Peet et al., 2001; Emsley et al., 2002; Berger et al., 2007), this has not been a consistent finding (Peet and Horrobin,

☆ This trial has been registered in the Iranian Registry of Clinical Trials (IRCT) with a registration number IRCT201603095280N23.

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2002; Fenton et al., 2001; Emsley et al., 2006). Bentsen et al., have reported an increase in symptoms associated with eicosapentaenoic acid (EPA), a specific n-3 FA used as an add-on therapy (Bentsen et al., 2013). Most studies have used EPA or ethyl ester of EPA as the n-3 FA intervention (Pawelczyk et al., 2015a).

Some antipsychotics drugs, specifically clozapine and olanzapine have been associated with overweight, dyslipidemia, hypertension and development of metabolic syndrome. Weight gain is also an adverse consequence of treatment with valproate sodium (VPA) and lithium (Li) (Faghihi et al., 2012).

N-3 PUFAs can additionally regulate the genes involved in lipid homeostasis (Eftekhari et al., 2014). Supplementation of omega-3 PUFAs in patients with hypertensive disease and metabolic syndrome lessens hyperlipidemia, has a moderate antihypertensive impact, and enhances endothelial function and microcirculation (Vasil'ev et al., 2009). N-3 PUFAs may be of value in patients taking clozapine and who have higher serum triglyceride levels (Caniato et al., 2006).

Consequently, the current study aimed to assess the impacts of n-3 PUFA supplements on metabolic and inflammatory indices by evaluating changes in weight, body mass index (BMI), waist circumference (WC), blood pressure (BP), serum hs-CRP and lipid profiles in a group of chronic schizophrenia patients from the Hejazi and Ibn Sina Hospitals in Mashhad who were on clozapine and valproate treatment for 3 months.

2. Methods

This study was approved by the Mashhad University of Medical Sciences Ethics Committee (ID number 921429) and has been registered in the Iranian Registry of Clinical Trials (IRCT) with a registration number IRCT201603095280N23. The study was compliant with the Treaty of Helsinki (1996) and the study protocol and consent form of ethics, confirmed by the committee of Mashhad University of Medical Sciences, were presented to the subjects before the start of the study. Written informed consent was obtained. The population consisted of patients diagnosed with schizophrenia who had been admitted to the Hejazi and Ibn Sina Hospitals between September 2014 to September 2015.

All patients who fulfilled the following criteria and were willing to participate in the project were included in the study: aged 18 or above who were treated with clozapine and valproate; and who had fasted serum triglycerides of < 499 mg/dl with normal other metabolic indices and who were normal before treatment with clozapine and valproate. The upper limit of 499 was chosen because levels higher than 500 mg/dl are a risk factor for medical complications such as pancreatitis and it was justified applying definitive treatment methods.

Subjects were randomly allocated to n-3 PUFA or placebo groups using random number tables (Fleiss, 1986). A double-blind trial design was used in which patients and the evaluators were not aware of the prescribed medications. Furthermore, it was also a prospective and randomized study based on variable blocks, which were applied to patients diagnosed with severe psychotic disorders.

2.1. Inclusion criteria

Inclusion criteria were: 1. Patients with schizophrenia who were treated with clozapine and valproate in the Ibn Sina and Hejazi Hospitals in Mashhad; 2. Patients aged 18 years or above; 3. Patients with fasted serum triglyceride levels < 499 mg/dl; 4. Patients with normal metabolic indices before the start of treatment with clozapine and valproate.

2.2. Exclusion criteria

Exclusion criteria were: 1. Breast-feeding or pregnant women; 2. A history of allergy to fish oil and any other contraindications to the medications prescribed in the study; 3. Intake of omega-3 FA over the last few months; 4. An obvious history of bleeding or a history of heparin or coumarin treatment; 5. Reluctance of patients to participate in the study; 6. Using other drugs such as statins; 7. A history of consuming or abusing alcohol or drugs within 6 months from baseline.

2.3. Study design

After completing the questionnaire, demographic features, anthropometric indices and some biochemical factors were measured. The laboratory evaluation was performed based on the clinical suspicion of a psychiatrist and neurologist and, if necessary, in consultation with a specialist in Internal Medicine to review an ECG. Considering the tolerance of patients and the emergence of side effects and therapy responses, the clozapine dose was increased up to 400 mg. All patients were on a stable dose of 300–400 mg of clozapine and 200–400 mg of valproate for 3 months. Then, each of these groups was randomly treated with either olive oil placebo (Pawelczyk et al., 2015a) or omega-3 PUFA, which was given to the patients by nurses who were blinded to treatment.

The participants received omega-3 FA, or placebo capsules (Drug Company) for 8 weeks. Each omega-3 FA capsule contains 1000 mg of omega-3, equivalent to 300 mg of EPA and DHA (180 mg EPA and 120 mg DHA). Initially, four capsules containing omega-3 FA and placebo were given to patients.

2.4. Measurements

Height, weight, abdominal circumference, serum fasted TG levels, total cholesterol, LDL-C, HDL-C, and Hs-CRP were determined at baseline and after 8 weeks of treatment. Weight was measured in the morning before breakfast. The patient's weight was determined while they were barefooted with light clothing, using a digital scale. The abdominal circumference was determined by placing a measuring device at the top of the iliac crest and the abdominal circumference was measured after expiration. To calculate BMI, weight (Kg) was divided by height squared (m^2).

FBG, total cholesterol and triglyceride (Pars Azmon Inc., Iran), LDL-C and HDL-C (Pishtaz Teb Inc., Iran) and Hs-CRP (Biosystem Inc, Spain), were measured using routine techniques on an auto-analyzer (Ependorf, Germany).

2.5. Statistical analysis

All data analyses were performed using the Statistical Package for Social Sciences (SPSS version 16). The normality of distribution was assessed by the Kolmogorov-Smirnov test. For normally distributed variables, the comparison between the groups was assessed by the Student's *t*-test for comparing the clinical characteristics and baseline demographics. Mann-Whitney *U* tests were used for non-normally distribute variables. Chi-square test, and/or Fisher exact test as appropriate. A linear regression was used to examine associations between weight with serum total cholesterol and FBG level. A *P* value of less than 0.05 was considered as statistically significant.

3. Results

Fifty-six subjects aged 18–60 years old were recruited in this study. Table 1 shows the baseline characteristics of participants. The study groups did not differ significantly in demographic and anthropometric indices, nor in serum FBG and Hs-CRP, before the intervention.

We found that taking n-3 PUFA was associated with an improvement in some anthropometric indices including weight ($p = 0.0001$), wrist circumference ($p = 0.009$), waist circumference ($p = 0.0001$) and BMI ($p = 0.011$), compared to the placebo group. Systolic and diastolic blood pressure, FBG, serum Hs-CRP and fasting lipid profile were not

Table 1
Baseline characteristics of participants.

Variables		Omega-3 Group	Placebo Group	*P*
Sex	Female % (*n*)	35.7 (10)	35.7 (10)	0.610
	Male % (*n*)	64.3. (18)	64.3. (18)	
Age(years)		37.21 ± 5.85	36.07 ± 7.90	0.051
Weight(kg)		72.5 ± 15.7	77.4 ± 9.5	0.166
Wrist circumference (cm)		19.30 ± 1.54	18.53 ± 1.55	0.104
Waist circumference (cm)		94.3 ± 24.7	101.0 ± 8.8	0.189
BMI(kg/m^2)		27.73 ± 4.95	27.30 ± 3.19	0.097
SBP(mmHg)		102.2 ± 9.5	101.6 ± 7.3	0.940
DBP(mmHg)		67.7 ± 7.7	68.9 ± 5.6	0.692
Serum TC(mg/dl)		216.6 ± 67.0	243.5 ± 52.3	0.094
Serum LDL-C(mg/dl)		145.8 ± 43.1	156.2 ± 37.4	0.798
Serum HDL-C(mg/dl)		37.7 ± 9.7	40.0 ± 8.6	0.349
Serum TG (mg/dl)		158.50(121.00–210.50)	203.0(161.0–286.2)	0.033
FBG(mg/dl)		95.5 ± 23.2	98.1 ± 20.3	0.825
Serum Hs-CRP(mg/l)		2.09(1.07–5.04)	2.00(0.58–5.80)	0.902

Values expressed as mean ± SD for normally distributed data, and median and interquartile range for non-normally distributed data. Between groups comparisons were assessed by parametric statistical analysis for normal distributed data and nonparametric test for non-normally distributed data. BMI: body mass index; SBP: Systolic blood pressure, DBP: Diastolic Blood Pressure, TC: Total Cholesterol, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, TG: Triglyceride, FBG: Fasting blood glucose, Hs-CRP: High-sensitivity C-reactive protein.

Table 2
Changes in parameters at baseline and after 8 weeks.

Changes in parameters at baseline and after 8 weeks intervention	Omega-3 Group	Placebo Group	*P*
Weight(kg)	−1.57 ± 3.13	0.64 ± 2.81	0.0001
Wrist circumference (cm)	−0.88 ± 1.09	−0.07 ± 0.71	0.009
Waist circumference (cm)	−4.78 ± 8.93	0.82 ± 3.34	0.0001
BMI(kg/m^2)	−0.77 ± 1.20	0.29 ± 0.56	0.006
SBP(mmHg)	2.32 ± 11.74	−0.89.1 ± 8.92	0.407
DBP(mmHg)	3.21 ± 10.55	2.14 ± 1.57	0.628
Serum TC(mg/dl)	−5.2 ± 73.63	4.14 ± 81.54	0.609
Serum LDL-C(mg/dl)	−15.42 ± 49.78	0.50 ± 62.18	0.228
Serum HDL-C(mg/dl)	−0.28 ± 10.94	−0.78 ± 12.02	0.778
Serum TG (mg/dl)	3.50(−34.50 to 43.00)	−9.50(−65.75 to 48.50)	0.491
FBG(mg/dl)	6.28 ± 25.70	−7.53 ± 33.11	0.235
Serum Hs-CRP(mg/l)	−0.70(−3.28 to 0.27)	−0.20(−1.87 to 0.99)	0.446

Values expressed as mean ± SD for normally distributed data, and median and interquartile range for non-normally distributed data. Between groups comparisons were assessed by parametric statistical analysis for normal distributed data and nonparametric test for non-normally distributed data. BMI: body mass index; SBP: Systolic blood pressure, DBP: Diastolic Blood Pressure, TC: Total Cholesterol, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, TG: Triglyceride, FBG: Fasting blood glucose, Hs-CRP: High-sensitivity C-reactive protein.

significantly affected by treatment with n-3 PUFA ($p > 0.05$ for all variables). Table 2 shows changes in the parameters from baseline to 8 weeks. According to the self-reported adverse effects, no side effects were observed in the current study.

As shown in Table 3, multivariate analysis has been done. Dependent variables in the logistic regression analysis were considered as a group variable (Placebo/Omega-3). All the variables that were statistically different in Table 2 were considered as predictors which were adjusted with respect to TG. Only waist circumferences changes remained statistically different after this adjustment.

3.1. Linear regression

As shown in Figs. 1 and 5, regression equations show that serum triglyceride and total cholesterol are decreased by weight augmentation after the intervention (β = −2.116, β = −1.651, respectively), (Figs. 1 and 5). (Figs. 2–4, Fig. 6)

Table 3
Multivariate logistic regression for group variable as a dependent.

	OR	*P*
Waist changes (cm)	3.800(1.11–12.99)	0.033
Weight changes (kg)	1.280(0.58–2.79)	0.536
Wrist changes (cm)	1.308(0.24–6.94)	0.753
BMI changes (kg/m^2)	1.700(0.25–11.16)	0.581
TGdiff (mg/dl)	1.002(0.98–1.02)	0.812
FBG changes (mg/dl)	0.986(0.94–1.02)	0.487
Constant	4.051	0.023

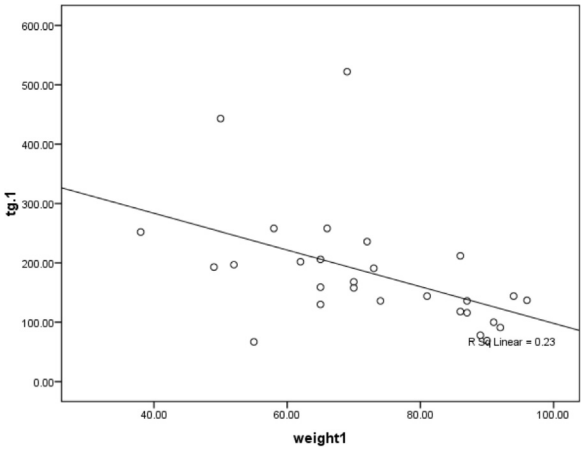

Fig. 1. Linear regression model for weight (kg) and serum triglyceride (mg/dl), before the intervention. The regression equation showed that serum triglyceride (tg) fell with increasing weight (β = −2.116, y = −2.116 + 315.57, R^2 = 0.23, df = 26, *P*-value = 0.002).

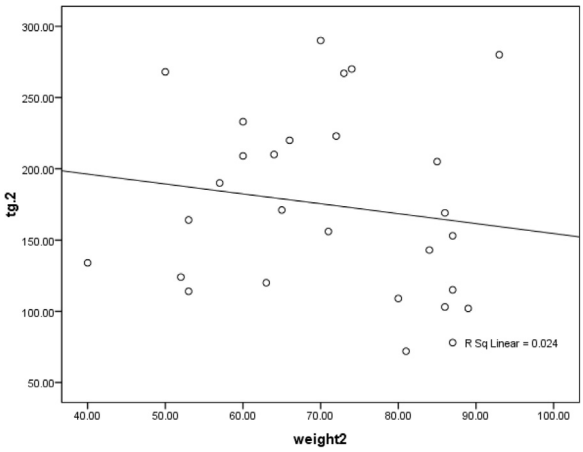

Fig. 2. Linear regression model for weight (kg) and serum triglyceride (mg/dl), after the intervention. The regression equation showed that serum triglyceride (tg) was not significantly related to weight (β = −0.695, y = −0.695x + 224.085, R^2 = 0.024, df = 26, *P*-value = 0.431).

4. Discussion

There was a significant improvement in waist circumference in patients with schizophrenia taking omega-3 capsules compared to those taking the placebo over a period of 8 weeks.

CHD is known to be a major cause of mortality in schizophrenia patients. The major risk factors for this increased mortality are obesity

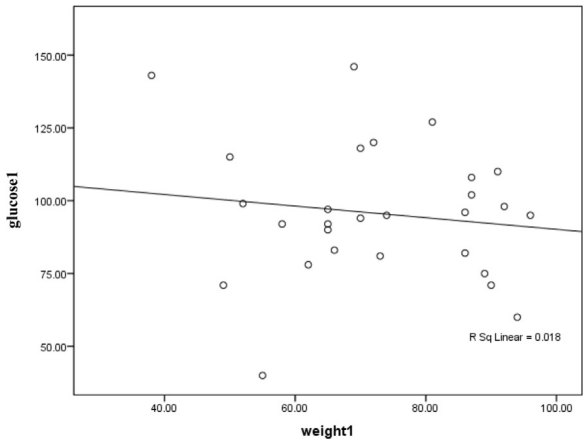

Fig. 3. Linear regression model for weight (kg) and fasting blood glucose (mg/dl), before the intervention. The regression equation showed that FBG was not significantly related to weight (β = −0.199, y = −0.199x + 110.113, R^2 = 0.018, df = 26, *P*-value = 0.493).

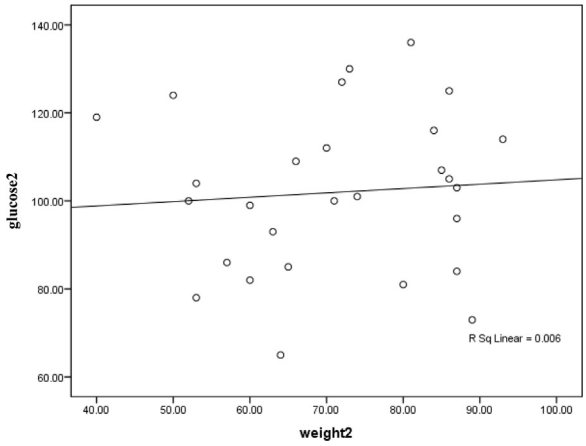

Fig. 4. Linear regression model for weight (kg) and fasting blood glucose (mg/dl), after the intervention. The regression equation showed that FBG was not significantly related to weight is decreased by weight augmentation (β = 0.099, y = 0.099x-94.90, R^2 = 0.006, df = 26, *P*-value = 0.693).

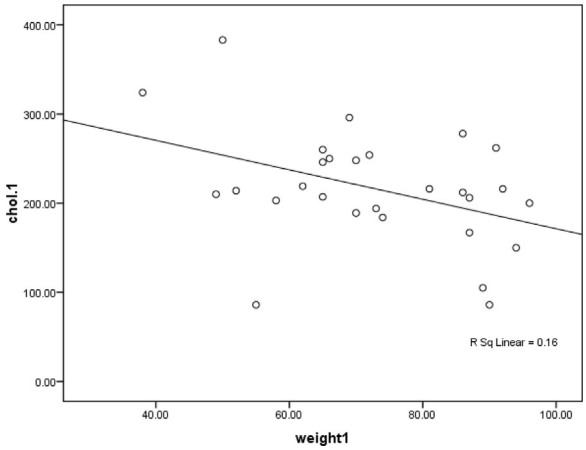

Fig. 5. Linear regression model for weight (kg) and total cholesterol (mg/dl) before the intervention. The regression equation showed that total cholesterol (TC) fell with increasing weight (β = −1.651, y = −1.651x + 336.42, R^2 = 0.16, df = 26, *P*-value = 0.035).

leading to dyslipidemia, smoking, increased blood pressure, diabetes and insulin resistance (Hennekens et al., 2005). Henderson et al., have shown that clozapine increase fat deposition around the waist in

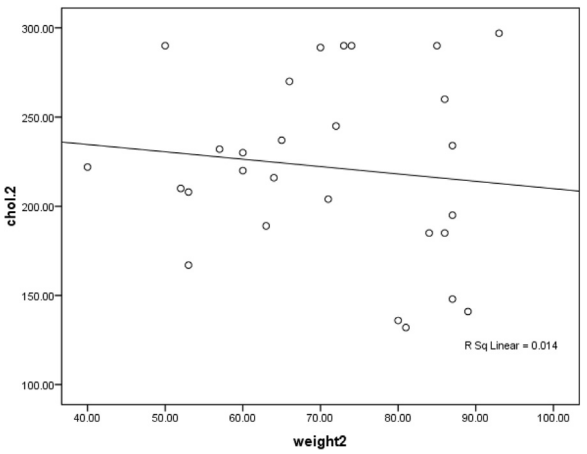

Fig. 6. Linear regression model for weight (kg) and total cholesterol (mg/dl) after the intervention. The regression equation showed that total cholesterol (TC) was unrelated to weight (β = −0.412, y = −0.412x + 251.118, R^2 = 0.014, df = 26, *P*-value = 0.552).

nonobese schizophrenia patients (Henderson et al., 2005). It has been reported that omega-3 fatty acid supplements can reduce the risk of coronary heart disease (CHD) (Harper and Jacobson, 2003), and that omega-3 fatty acids level is lower than average concentration in patients with schizophrenia (Richardson et al., 2003).

Our results showed omega-3 supplementation does not improve FBG concentration in patients with schizophrenia. Faghihi et al. reported that glucose-insulin homeostasis was not improved by omega-3 capsules for 6 weeks in patients with schizophrenia receiving olanzapine combination therapy with valproate or lithium. There were no any significant changes in FBG, fasting insulin, HbA1c and HOMA-IR levels in these patients (Toktam et al., 2010). It has also been shown that eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) supplements can reduce serum concentrations of several cytokines inflammatory markers, for example, IL-1, IL-6 and TNF-α (Faghihi et al., 2012). But in another study, treatment with omega-3 unsaturated fats had no significant effect on serum hs-CRP levels in both healthy subjects and in patients with stable CAD, and reduced triglyceride levels in healthy subjects but not in patients with CAD (Burns et al., 2007). It has been reported that the composition of mixed omega 3 unsaturated fats (particularly the proportion of EPA/DHA) can impact on glucose control and lipid levels in patients with Type 2 Diabetes (Chen et al., 2015). We did not find any positive effect on these factors in the current study.

We have found some positive effects of omega-3 FA supplements on anthropometric indices in patients with schizophrenia taking clozapine and sodium valproate. Most omega-3 trials (Bentsen et al., 2013; Amminger, 2010) have previously focused on measuring the effectiveness of omega-3 on symptom severity of patients with schizophrenia using the Positive and Negative Syndrome Scale (PANSS). It has been shown that omega-3 PUFA have beneficial efficacy in patients with schizophrenia (Peet et al., 2001; Berger et al., 2007). Although, the results of these studies have been inconsistent. Some other trials have reported negative findings (Peet and Horrobin 2002; Fenton et al., 2001; Emsley et al., 2006). Bentsen et al., reported an increase in symptomatology associated with EPA add-on therapy (Bentsen et al., 2013). The intervention period in most studies was 8–12 weeks. The longest period for the omega-3 intervention was 12 months (Amminger et al., 2010). Amminger et al. (2010) showed that omega-3 intervention for a period of 12 weeks decreased the transition rate to psychosis. Moreover, it cause to symptomatic and functional improvements in subjects at ultra-high risk of psychosis during the 12 months follow-up period (Amminger et al., 2010).

4.1. Conclusion

Our results showed omega-3 supplementation in 8 weeks can improve some anthropometric indices in patients with schizophrenia who taking clozapine pharmacotherapy.

4.2. Study limitations

The current study lacks any information on dietary intake of the subjects. This can have a significant effect on the interpretation of our data. Moreover, high serum triglycerides were associated with low weight. It may be that the hypertriglyceridemic subjects, who were more obese, were taking drugs for their dyslipidaemia, or had different dietary intakes.

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Conflict of interest

The authors have no interest to declare.

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