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Long-Term Variations of Antithyroperoxidase Antibodies and its Clinical Significance

Authors
Masoumeh Keyhanian[1 *], Farzaneh Sarvghadi[1 *], Ladan Mehran[1], Atieh Amouzegar[1], Maani Beigy[1], Maryam Tohidi[2], Fereidoun Azizi[1]

Affiliations
1 Endocrine Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, I. R. Iran
2 Prevention of Metabolic Disorders Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, I. R. Iran

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Correspondence
Fereidoun Azizi
Professor of Internal Medicine and Endocrinology
Endocrine Research Center
Research Institute for Endocrine Sciences
Shahid Beheshti University of Medical Sciences
P. O. Box: 19395–4763
Tehran, I. R. Iran
Tel.: + 98/21/22432 503, Fax: + 98/21/22402 463
azizi@endocrine.ac.ir

Ladan Mehran MD, PhD
Research Associate in Endocrinology
Endocrine Research Center
Research Institute for Endocrine Sciences
Shahid Beheshti University of Medical Sciences
P. O. Box: 19395–4763
Tehran, I. R. Iran
lmehran@endocrine.ac.ir

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ABSTRACT

Various cut-offs have been proposed for thyroid peroxidase antibodies (TPOAb) positivity. Considering that the long-term trend of TPOAb levels and its positivity incidence is not clearly understood, we conducted the current study to determine the longitudinal variations of TPOAb in a population-based cohort study. We followed 5783 individuals of Tehran Thyroid cohort Study (TTS) for 10 years (4 phases). After exclusions, data of 3493 euthyroid participants remained for analyses. The baseline prevalence rates of TPOAb positivity were 19.8, 17, and 11.4 % and the annual incidence rates (95 % CI) of TPOAb positivity were 8.53 (8.29–8.77), 7.59 (7.37–7.80) and 6.79 (6.60–6.98) per 1000 persons for the 3 proposed cut-offs of 14.77, 18.38, and 40 U/l; respectively. Although a slightly increasing trend was observed for TPOAb levels ($p = 0.001$) and its conventional positivity (TPOAb > 40U/l), the recently proposed cut-offs of 14.77 and 18.38 U/l showed constant TPOAb positivity over 10 years. The time trends of the TPOAb levels among younger participants were significantly different from older participants (time × age effect $p = 0.004$), with the former having an increasing trend and the latter, a relatively decreasing trend. Although the prevalence of TPOAb positivity was significantly ($p < 0.001$) higher among women as compared to men, the longitudinal changes of TPOAb were similar in men and women. TPOAb positivity along with TSH values between 2.5 and 5.0 mU/l or free T4 values between 0.93 and 1.7 ng/dl exerted a significantly increased risk of subclinical or overt hypothyroidism. In an iodine sufficient population, an increasing trend in TPOAb levels was observed in line with the increasing incidence of subclinical and overt hypothyroidism.

* KM and SF are co-first authors as they contributed equally to this manuscript.

Introduction

Autoimmunity plays important roles in thyroid diseases, in which abnormal immune responses directed to thyroid-related proteins culminate in 2 opposite pathogenic processes, including Graves' disease and Hashimoto thyroiditis [1]. Hypothyroidism results from insufficient thyroid hormone function and has generally an incidence of 2 % in adult women, being less common in men [2, 3]. Iodine deficiency has been the most common cause of hypothyroidism worldwide [4], but in countries with sufficient iodine intake, Hashimoto thyroiditis is its most prevalent cause [5]. On the contrary, hyperthyroidism is manifested as hyper-function of the thyroid gland, characterized by increased basal metabolism and disturbances in the autonomic nervous system [6]. Its incidence is higher in women (2 %) than in men (0.02 %). Several conditions like diffuse toxic goiter or Graves' disease, toxic nodular goiter, toxic adenoma, therapy-induced hyperthyroidism, excess iodine intake, thyroiditis, follicular carcinoma, and TSH-producing tumors of the pituitary might be the underlying cause [6].

More than 95 percent of individuals diagnosed with Hashimoto's thyroiditis and nearly over 75 percent of those with Graves'disease have detectable antibodies targeting the thyroid peroxidase enzyme, that is, thyroid peroxidase antibodies (TPOAb) [7]. Therefore, various cut-offs have been proposed for detection of TPOAb positivity which are used to predict the incidence of autoimmune thyroid disease (AITD) in healthy individuals, considering the importance of AITD for early diagnosis of hypothyroidism as a consequence of Hashimoto's thyroiditis [8, 9]. The twenty-year follow-up of the Whickham survey showed an association between the development of goiter and thyroid antibody status in women at follow-ups, but not initially [10]. The risk of developing hypothyroidism has been demonstrated to be increased with raised serum TSH, having positive antithyroid antibodies and female gender [10, 11]. Participants with positive TPOAb are demonstrated to be more likely to develop thyroid dysfunctions [11, 12]. Thyroid antibodies are more prevalent in women than men and increase with age. TPOAb is significantly associated with hypo- or hyperthyroidism, whereas TgAb is not [11]. Moreover, TSH cutoffs of 2.5 and 4.0 $mU \cdot l^{-1}$ combined with TPOAb above 29 $IU \cdot l^{-1}$ have been suggested for the estimation of long-term risk of incident hypothyroidism [13].

Our national reference ranges of thyroid function [14] and TPOAb levels [9], and their regression dilution bias [15] have been recently defined. Although data regarding TPO antibody levels and the relation with sex, age, etc. are well-known in the literature, the longitudinal variations in TPOAb positivity and its clinical importance are not well understood and there are still questions that remain to be answered. We do not know how much the TPOAb positivity varies throughout the age-sex cohorts and whether this change is remarkably different across the various TPOAb cut-off points. Considering the long-standing debate of widespread screening of general populations regarding the thyroid function and thyroid antibodies [16], we aimed to investigate 10-year variations in TPOAb among individuals of a population-based cohort study, in line with other predictive variables.

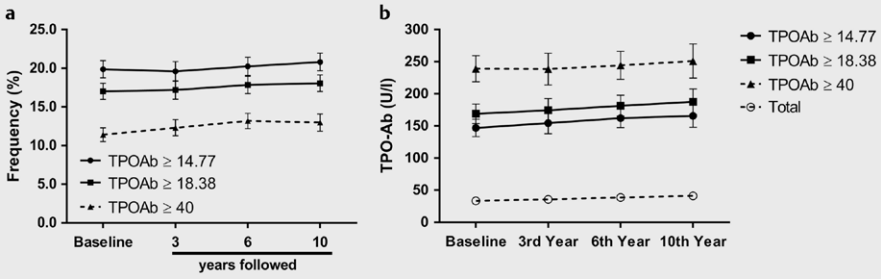
Subjects and Methods

Tehran Thyroid Study (TTS) is a community-based cohort study, being performed on the residents of district 13 of Tehran with the aim of evaluating the incidence and natural course of thyroid diseases and their long-term outcomes in the urban, iodine sufficient population of Tehran [17], the capital of Iran. Details of the study methods have previously been described [18]. TTS was conducted within the framework of Tehran Lipid and Glucose Study (TLGS) [19], in which 15 005 residents aged ≥ 3 years participated. Data collection is ongoing, designed to continue for at least 20 years, at 3-year intervals. Among participants aged ≥ 20, those who participated in the follow-up study (n = 5783) until 20 March 2009 were selected for TTS. Written informed consent was obtained from all participants, and the protocols of this study were approved by the ethics committee of the Research Institute for Endocrine Sciences.

Participants were excluded based on the following criteria: Elevated baseline TSH and decreased free T4; taking levothyroxine or antithyroid drugs; TSH levels < 0.1 $mIU \cdot l^{-1}$; taking amiodarone, lithium, glucocorticoids, or IFN-α; having undergone thyroidectomy or radioactive iodine therapy; or pregnancy. After exclusions, 5783 individuals remained for the time trend study. At the time of the present analyses, the median follow up time was 9.73 years. Information regarding results of participants' examinations was documented.

Clinical and laboratory measurements

One trained interviewer collected data including demographic data, family history of premature CVD, past medical history of CVD, and smoking status. Weight was determined, when participants were minimally clothed without shoes, by a digital scale (Seca 707: range 0.1–150 kg) and recorded to the nearest 100 g. We measured height in a standing position without shoes, by tape meter with shoulders in normal alignment. An un-stretched tape meter was used to determine the waist circumference (WC) at the umbilical level; hip circumference (HiC) was measured at the maximum level over light clothing, without any pressures to body surface, and measurements were recorded to the nearest 0.1 cm. Body mass index (BMI; $kg \cdot m^2$) was calculated as weight (kg) divided by square of the height (m^2). We calculated waist to hip ratio (WHR) as WC (cm) divided by HiC (cm), and waist to height ratio (WHtR) was calculated as WC (cm) divided by height (cm). Systolic and diastolic blood pressures (SBP and DBP) were measured twice after 15 min rest in the sitting position; 2 measurements were taken, using a standardized mercury sphygmomanometer (calibrated by the Iranian Institute of Standards and Industrial Researches) and the average of the 2 measurements was calculated as the participants' blood pressure. Blood samples were obtained between 7:00 and 9:00 AM from all participants, after 12–14 h overnight fasting. All of the blood analyses were performed at the TLGS research laboratory on the day of blood collection. FT4 and TSH were assayed on −70 °C stored serum samples by the electrochemiluminescence immunoassay (ECLIA) method, using Roche Diagnostics kits and Roche/HitachiCobas e-411 analyzer (GmbH, Mannheim, Germany). Lyophilized quality control material (Lyphochek Immunoassay plus Control, Bio-Rad Laboratories) was employed to monitor the accuracy of the assays; the intra- and inter-assay CVs were 1.5 and 4.5 % for TSH and 1.3 and 3.7 % for FT4, respectively. TPOAb was measured by the immune enzyme metric assay



▶ **Fig. 1** Time trend of the prevalence rate of high TPOAb status **a** and its levels expressed as mean with 95 % confidence interval **b**. Significant time effect (p = 0.001) was observed for longitudinal changes of TPOAb.

(IEMA) kit (Monobind, Costa Mesa, CA, USA) and the Sunrise ELISA reader (Tecan Co., Salzburg, Austria); with intra- and inter-assay CVs of 3.9 and 4.7 %, respectively [20].

Definition of terms

We defined current smoker as a person who smokes cigarettes daily or on occasions. Participants were categorized into younger and older on the basis of the cutoff point of 50 years. Based on previous studies we defined TPOAb positivity as ≥ 40 U/l [21, 22]. Moreover, based on the TTS optimal cut-offs of TPOAb for prediction of SH and Hypo, we defined ≥ 14.77 U/l and ≥ 18.38 U/l [9] as high TPOAb levels.

Levels of FT4 were categorized using cutoff points of 0.93 and 1.55 ng · dl^{-1}, and those of TSH at cutoff points of 0.3, 2.5, and 5.0 mIU · l^{-1}, based on the previous studies [13]. Subclinical hypothyroidism was defined as serum TSH levels > 5.06 mIU/l with normal FT4 level. Overt hypothyroidism was defined as serum TSH levels > 5.06 mIU/l and FT4 < 0.91 ng/dl. Subclinical hyperthyroidism was defined as serum TSH level < 0.34 mIU/l and normal FT4 level. Overt hyperthyroidism was defined as a TSH concentration < 0.34 mIU/l with serum FT4 concentration > 1.55 ng/dl [23].

Statistical methods

Findings on covariates are expressed as means (SD) or percentages for continuously- and categorically-distributed variables, respectively. Incidence rates of TPOAb positivity and subclinical hypo- and clinical hypothyroidism were estimated per 1000 person-years with 95 % confidence intervals. The randomness of missing data and loss to follow-up was tested before analyses. For those individuals with some data in follow-up but not having completed the 10-year follow-up or having serious missing data, we included their person-time data in the computation of incidence rates.

Also, relative risks (RR) with 95 % confidence intervals were used to describe the predictive importance of TPOAb positivity for incidence of progression to subclinical hypo- and clinical hypothyroidism, as compared with euthyroid persistency after 10 years of follow-up. Repeated-measures ANOVA test was performed to investigate the longitudinal changes of TPOAb over 10 years of follow-up. We defined the statistical significance level at a 2-tailed type I error of 0.05. All statistical analyses were performed using STATA version 12 (STATA, College Station, Texas USA).

Results

After applying the exclusion criteria, from the total of 5783 euthyroid cases (2376 male, 3407 female) followed for 10 years, 3493 euthyroid subjects remained for analysis. Data of excluded individuals are shown in ▶ **Fig. 1S**. Among the initial 5783 participants, only 4.23 % of subjects developed overt abnormal thyroid function and were excluded. Mean age of men and women at baseline were 41.1 and 39.3 years, respectively.

The annual incidence rates (95 % CI) of TPOAb positivity were 8.53 (8.29–8.77), 7.59 (7.37–7.80), 6.79 (6.60–6.98) per 1000 persons for the 3 proposed cut-offs of 14.77 U/l, 18.38 U/l, and 40 U/l, respectively. The baseline prevalence rates of TPOAb positivity were 19.8, 17, and 11.4 % for the cut-offs of 14.77, 18.38, and 40 U/l, respectively.

Longitudinal changes of TPOAb positivity and its levels are shown in ▶ **Fig. 1**. Significant time effect (p = 0.001) was observed for longitudinal changes of TPOAb and its conventional positivity (TPOAb > 40 U/l) during 10 years. However, the recently proposed cut-offs of 14.77 and 18.38 U/l showed constant TPOAb positivity over 10 years. The time trend of the TPOAb positivity categorized by age and sex is shown in ▶ **Fig. 2S**. The longitudinal variations of the TPOAb levels among younger participants (< 50 years) were significantly different from those of older participants (time × age effect p = 0.004), with the former having an increasing trend and the latter (≥ 50 years) relatively decreasing trend. Although the prevalence of TPOAb positivity was significantly (p < 0.001) higher among women as compared to men, the time trends of TPOAb were the same among men and women.

▶ **Fig. 4S** shows the time trend of TPOAb positivity by smoking staus. Longitudinal variations of TPOAb positivity were not significantly different between smokers and nonsmokers.

The risk associated with TPOAb positivity for progression from euthyroidism to clinical and subclinical hypothyroidism after 10 years is shown in ▶ **Table 1S**. We observe that TPOAb ≥ 14.77 U/l exert a significant risk for both SH (p < 0.001; RR 95 % CI = 2.91, 2.11–4) and Hypo (p < 0.001; RR 95 % CI = 8.94, 4.73–16.88). Also, TPOAb ≥ 18.38 U/l exerted a significant risk for both SH (p < 0.001; RR 95 % CI = 3.29, 2.36–4.58) and Hypo (p < 0.001; RR 95 % CI = 8.68, 4.65–16.21). Similarly, TPOAb ≥ 40 U/l demonstrated a significant risk for both SH (p < 0.001; RR 95 % CI = 3.51, 2.42–5.1) and Hypo (p < 0.001; RR 95 % CI = 8.86, 4.68–16.74). According to the overlapped CI of these RRs (▶ **Table 1S**), the risks indicated by various cut-offs of TPOAb positivity did not differ. Moreover, the multivar-

iate models showed that the effects of TPOAb positivity on progression to SH and Hypo were not significantly different after adjustment for the effects of age, gender, and smoking (▶ **Table 1S**).

▶ **Table 2S** shows the annual incidence rates of subclinical hypothyroidism and clinical hypothyroidism by varying levels of TSH and TPOAb. According to these findings, regardless of the TSH levels, the incidence of hypothyroidism was higher among those with positive TPOAb compared to those with negative TPOAb. Moreover, TPOAb positivity along with TSH values between 2.5 and 5.0 (mIU/l) showed a significantly increased risk of subclinical or overt hypothyroidism, as compared to lower levels of TSH.

The annual incidence rates of subclinical hypothyroidism and clinical hypothyroidism by varying levels of FT4 and TPOAb are also illustrated in ▶ **Table 3S**. We observed that among patients with FT4 levels between 0.93–1.7, the risk of progression to hypothyroidism was more prominently indicated by positive TPOAb, as compared to those with negative TPOAb. The non-linear association between TPOAb levels and age are depicted in ▶ **Fig. 4S**.

Discussion

Using data form a large prospective community-based cohort; this is one of the first studies to assess the time trends in the TPOAb levels and its positivity according to the various proposed cut-offs. No significant difference was observed in the relative risk and incidence rate derived from conventional cutoff point of 40 mU/l with the cut-offs defined in TTS. Population levels of the TPOAb were slightly increased over 10 years. Baseline prevalence rates of TPOAb positivity were 19.8, 17, and 11.4 % for the cut-offs of 14.77, 18.38, and 40 U/l; respectively. Incidence rates of TPOAb positivity were 8.53, 7.59, 6.79 per 1000 person/years for the three proposed cut-offs of 14.77, 18.38 and 40 U/l, respectively. Age was observed to modify the steepness of the slope of TPOAb so that younger individuals showed an increasing trend whereas older individuals showed a relatively decreasing trend. TPOAb positivity along with TSH values between 2.5 and 5.0 (mIU/l) showed a significantly increased risk of subclinical or overt hypothyroidism, as compared to lower levels of TSH.

Studies reporting the association of smoking with thyroid autoimmunity are controversial, many reporting the reduced risk of thyroid autoimmunity in smokers, which may be due to decreased TSH secretion, inhibition of prostaglandin synthesis, the interference of smoke with iodide transport and organification or decreased hormonal and cell mediated immunity [24, 25]. Autoimmune response to thyroid cells is developed under the effect of susceptibility genes and their interaction with environmental triggers including iodine [26, 27], medications, infection, smoking, stress, irradiation, pollutants, pregnancy, parity and geographic variations [28, 29]. However, as disease may be associated with a combination of factors manifesting over a long time, it is often difficult to directly link an environmental factor with thyroid autoimmunity. Therefore trend of TPOAb in a population may vary based on the circumstances of environmental factors over time.

The association of age with a biomarker investigated in a cross-sectional study could be flawed by the differences in the chronological exposure; in other words, the age-biomarker association investigated in a cross-sectional study might be merely a reflection of difference in levels of exposure to an environmental factor that has changed over time. As such, the amount of variation in the biomarker of interest explained by variation in age is simply representation of variations in the time-dependent level of exposure to a certain environmental factor [30]. In other words, age is very likely to confound the effect on an outcome of time-varying variables. These associations were found in cross-sectional surveys [31, 32]. In view of the confounding effect of age, the question arises whether such an age-thyroid function relation could still hold in longitudinal analyses.

Since, the association of aging with an increased prevalence of thyroid autoantibodies and subclinical hypothyroidism has been reported, the decreasing trend of TPOAb in older subjects ≥ 50 was an unexpected finding. Although thyroid autoantibodies are frequently reported in hospitalized or unselected elderly subjects, their presence are rare in centenarians and in highly selected aged populations, which suggest that thyroid autoimmunity is not the consequence of the aging process itself, but rather an expression of age-associated disease [33]. On the other hand, the elderly population with thyroid dysfunction were excluded, this may have caused some decrease in the prevalence of TPOAb positivity.

Also iodine supplementation in previously deficient communities has been linked to the induction of thyroid autoimmunity [34–36]. Mechanisms by which iodine can induce thyroid autoimmunity include the direct toxic effects of iodine on thyrocytes by generating free oxygen radicals, increased immunogenicity of highly iodinated Tg and the direct stimulation of immune responses to the thyroid [37]. In Iran prior to 1993 many areas were affected by moderate to severe iodine deficiency and universal salt iodization was implemented from 1996, with Iran being declared to be IDD-free since 2000 [17]. Observational studies have demonstrated increased incidence of autoimmune thyroiditis in regions with increased iodine intake compared to regions of low iodine intake [38]; in a 5-year cohort of 3018 Chinese subjects, the incidence of subclinical hypothyroidism and autoimmune thyroiditis was higher in individuals with higher median urinary iodine [38]. Moreover, an increased prevalence of Hashimoto's thyroiditis was reported after correction of iodine deficiency [39]. Kahaly et al. followed two groups of patients with endemic goiter, one that received iodine for 6 months and the other that received T4 and they found higher titers of thyroid autoantibodies in 19 % of the patients receiving iodine, which decreased significantly after iodine withdrawal [40]. Therefore, thyroid autoimmunity associated with iodine nutrition, may be a transient phenomenon. Burek et al. reported that the increased incidence of thyroiditis in NOD.H2 h4 mice after adding excess iodine to their water [41], indicating that iodine supplementation and other environmental and genetic factors and their interaction may paly role in the trend of TPOAb over time.

The 20-year follow-up of the Whickham cohort provided incidence data and allowed the determination of risk factors for spontaneous hypothyroidism in this period [10]. Either raised serum TSH or positive thyroid antibodies, whether each per se, were associated with a significantly increased risk of developing hypothyroidism; the risk of incident hypothyroidism at follow-up was examined with respect to risk factors identified in the first survey. The odds ratios (95 % CIs) of developing hypothyroidism with positive TPOAb per se were 8 (5–15) for women and 25 (10–63) for men; for both increased serum TSH and positive antithyroid antibodies

were 38 (22–65) for women and 173 (81–370) for men. Our results support such findings (▶ **Tables 1** and ▶ **2**). However, lower risk reported in TTS may be due to different prospective designs, as the TTS follow-ups were at 3 year intervals, whereas in the Wickham survey only first and last follow-up were considered. On the other hand, the hemagglutination technique in the Wickhham had less sensitivity in comparison with the highly sensitive laboratory kits with better CVs in TTS; also in TTS measurements in all 4 follow-ups were obtained on the frozen samples at the same time. In the NHANES III survey, TPOAb similarly predicted the risk of developing hypothyroidism [11, 42]. All studies indicate that the higher the serum TSH value, the greater the likelihood of development of overt hypothyroidism in subjects with chronic autoimmune thyroiditis. In women, an association was found between the development of a goiter and thyroid-antibody status at follow-up, but not initially [10]. The goiter was not considered in the current analysis.

Based on the previous studies TPOAb positivity defines as ≥ 40 U/l [21, 22]. In the population of TTS (representative for Iranian population), optimal TPOAb cut-offs for prediction of subclinical and clinical hypothyroidism are defined as ≥ 14.77 U/l and ≥ 18.38 U/l, respectively [9]; therefore, these cut-offs are known as the population specific cut-offs points for positive TPOAb levels in TTS. The cut-offs of 14.7 and 18.3 are more suitable to use in Iranian population as these cut-offs are specific for this population and are associated with significant higher prevalence of subclinical and clinical hypothyroidism compared with traditional general cut-offs of 40, however there are no significant differences in the relative risk of hypothyroidism among these cut-offs.

To the best of our knowledge no other study has ever reported the seroconversion rate in terms of TPOAb, previously. Having younger age, female gender, and subclinical hypothyroidism were all observed to independently accelerate the pace by which participants might have progressed to high TPOAb status. The strongest predictor of the incidence rate of seroconversion to a high TPOAb status was baseline TPOAb titers. Baseline TPOAb levels were associated with the high TPOAb seroconversion rate in a parabolic fashion. The high TPOAb seroconversion rate was inversely associated with age in a quadratic or hyperbolic fashion. Generally the optimal cut-off values of 14.77 and 18.38 have been recently proposed for SH and clinical hypothyroidism, respectively[9].

The strengths of our prospective study lies in its population-based nature of the study and the longitudinal nature with long-term follow up period. Our findings, however, needs to be interpreted in light of its limitations, among which the most important was lack of statistical power in the subgroup analysis; the natural course of goiter was not studied in the current study and at last other anti-thyroid antibodies, such as TSH receptor antibody were not measured.

Conclusion

In summary, this prospective community-based 10-year cohort of an iodine sufficient population shows an increasing trend in TPOAb levels in line with the increasing incidence of hypothyroidism. The recently proposed cut-offs of 14.77 and 18.38 U/l showed 19.8 % and 17 % TPOAb positivity, which is significantly higher than the conventional cut-off (40 U/l). These new cut-off seemed to be more robust during 10 years of follow-up, although the conventional cut-off (40 U/l) did show time-related variation. Age was observed to modify the steepness of the slope of TPOAb so that younger individuals showed an increasing trend, while older individuals showed a relatively decreasing trend over time. TPOAb positivity along with TSH values between 2.5 and 5.0 (mIU/l) showed a significantly increased risk of subclinical or overt hypothyroidism, as compared to lower levels of TSH.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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