Does Obstructive Sleep Apnea Treatment Influence Lipoprotein (a) Concentrations? Data from the TREATOSA-MS Clinical Trial

To the Editor:

Lipoprotein (a) (Lp[a]) is a highly atherogenic molecule similar to low-density lipoprotein; it is formed by the union of apolipoproteins B-100 and A (1). Several lines of evidence suggest that Lp(a) contributes to cardiovascular events, regardless of other traditional risk factors (1–3).

Obstructive sleep apnea (OSA) has been considered a potential nontraditional risk factor for increasing cardiovascular risk, and available evidence supports that this risk is partially explained by metabolic deregulation (4–6). Cross-sectional studies suggested that OSA is associated with increased Lp(a) concentrations (7, 8). However, the results are conflicting (9), and the nature of cross-sectional studies precludes definitive conclusions, especially in the context of the significant contribution of genetics in determining Lp(a) concentrations (10). Therefore, it is potentially relevant to understand the effects of OSA treatment on Lp(a) concentrations. We hypothesized that effective treatment of OSA would promote a significant decrease in Lp(a) concentration compared with placebo.

Methods

In this subanalysis of a randomized controlled trial of the TREATOSA-MS (Impact of Obstructive Sleep Apnea Treatment in Patients With Metabolic Syndrome) study (ClinicalTrials.gov identifier NCT 02295202) (5, 6), we recruited patients with metabolic syndrome (MS) and moderate to severe OSA (apnea–hypopnea index $\geq$ 15 events/h) to undergo 6 months of treatment with continuous positive airway pressure (CPAP) or a nasal dilator (placebo group). Informed consent was obtained from each patient, and the study protocol conforms to the ethical guidelines of the Declaration of Helsinki of 1975, as reflected in *a priori* approval by the institution's human research committee.

All patients were recently diagnosed, sedentary nonsmokers who did not use medications. No dietary recommendations were made during the study. Before and after randomization to each intervention, we performed a clinical evaluation and blood sample collection. Lp(a) was measured using a fully automated particle-enhanced turbidimetric immunoassay (Roche Diagnostics). A single researcher who was blinded to the group allocation performed all analyses.

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Statistical Analysis

As previously described (5), statistical analyses were performed using R 3.6.0 software (R Core Team). Data are expressed as mean $\pm$ standard deviation, median (interquartile range), absolute frequency, and relative frequency, as appropriate. The delta variations (postintervention minus preintervention) for each group and between groups were compared using the nonparametric Mann-Whitney test. Intergroup comparisons of Lp(a) changes were adjusted for baseline values (to avoid effects arising from regression to the mean). Significance was assessed with a P value <0.05.

Results

Following the intention-to-treat principle, 94 patients ($n = 47$ in each group) were randomized (80% men, age 48 $\pm$ 9 years, body mass index 33 $\pm$ 3 kg/m^2, apnea–hypopnea index 59 $\pm$ 29 events/h). Six patients from the original study had no available samples for analysis. As previously reported (5), there were no differences in baseline body mass index, neck and waist circumferences, and baseline visceral fat between the CPAP and nasal dilator groups.

Mean adherence to CPAP was 5.3 $\pm$ 1.8 h/night. There were no significant changes in median (interquartile range) Lp(a) between the baseline and follow-up periods in each group (placebo: baseline, 11.0 [7.0–41.0] nmol/L; 6 months, 11.5 [7.0–42.8] nmol/L [$P = 0.808$]; CPAP: baseline, 21.0 [7.0–69.0] nmol/L; 6 months, 20.5 [7.0–76.5] nmol/L [$P = 0.160$]). Similarly, we found no effect of CPAP treatment versus placebo on Lp(a) concentrations ($P = 0.198$; Figure 1). There were no significant differences in total or low-density lipoprotein cholesterol between the groups (data not shown).

Discussion

Lp(a) has attracted enormous interest, serving as a new biomarker of cardiovascular risk (3). Therefore, understanding medical conditions associated with increased Lp(a) concentrations is desirable. Previous evidence pointed out that MS is a comorbidity associated with increased Lp(a) concentrations (11). OSA is common in patients with MS (12, 13) and may influence the metabolic deregulation observed in these patients. Indeed, our previous investigation showed that CPAP could reverse MS at a higher rate than observed in the placebo group (5). On the basis of previous evidence suggesting that OSA may be related to Lp(a) concentrations (7, 8), the rationale for exploring the impact of treating OSA in patients with comorbid MS is justified. In this investigation, 6 months of good CPAP use did not influence Lp(a) concentrations compared with placebo.

Strengths and Limitations

Strengths of this study include its robust design, the good CPAP compliance, lack of any medications (some of which may influence Lp[a] concentrations) (14), and blinded assessments of Lp(a) by a

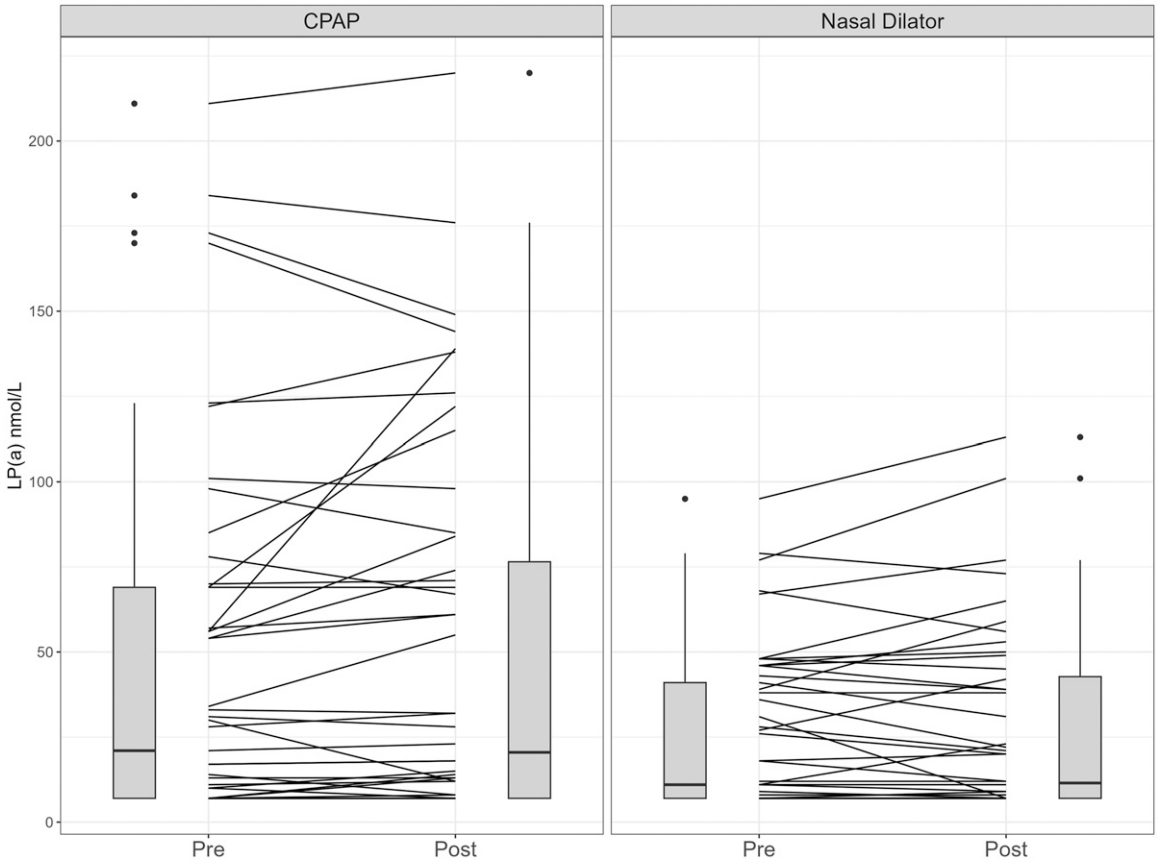

Figure 1. The effect of 6 months of CPAP versus nasal dilator (placebo) on lipoprotein (a) (Lp[a]) concentrations. Individual values for Lp(a) concentrations in all patients are shown. There were no significant changes in Lp(a) concentrations between groups. CPAP = continuous positive airway pressure.

single investigator. Nevertheless, there were some limitations that deserve comments. The study was not specifically designed to evaluate the effects of Lp(a) concentrations; however, because the TREATOSA-MS trial was designed to assess several metabolic parameters, our standardized protocol for sample collection and storage, the stringent inclusion criteria, and the lack of potential confounders (including medications) mitigated this limitation. Although patients with MS frequently have moderate to high cardiovascular risk, Lp(a) concentrations are often measured in very high risk patients, including those with coronary artery disease and previous myocardial infarction (2). Therefore, our population may not be ideal for studying Lp(a), despite the lipid impairment related to the MS diagnosis.

Conclusions

OSA appears not to influence Lp(a) concentrations. Although some nongenetic factors may influence Lp(a) (including MS) (10), these findings reinforce that Lp(a) concentrations are controlled predominantly by genetics (2, 10). Our findings highlight the need for specific therapies rather than control of cardiovascular risk factors targeting Lp(a) concentrations. Future studies focusing on exploring the impact of OSA only in patients with very high concentrations of Lp(a) are warranted. ■

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