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Tirzepatide for OSA and obesity: do we know the effect on cardiometabolic outcome?

Zachary T. Bloomgarden

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A recent study reassessed aspects of the SURMOUNT-OSA study of people with obstructive sleep apnea (OSA) treated for 52 weeks with tirzepatide *vs*. placebo, asking the question of the extent to which improvement in cardiometabolic risk factors could be attributed to weight loss, to improvement in OSA parameters, or to the combination of both factors[1]. It is instructive to examine the fashion in which the analysis was conducted and the limitations of the study itself to ascertain whether we now can satisfactorily answer the basic question addressed.

The study recruited 469 people with an apnea-hypopnea index (AHI) ≥ 15 events per hour and body mass index (BMI) ≥ 30 kg/m^2, randomized to tirzepatide 10-15 mg weekly or placebo; approximately half of the participants had baseline and ongoing use of positive airway pressure (PAP) therapy and half did not, so rather than randomization to PAP *vs*. non-PAP the two sets of patients were examined for effect of tirzepatide in parallel. Varying somewhat with use of PAP, the baseline BMI was ~39 kg/m^2, and the baseline AHI was ~50 events per hour. Individuals with diabetes were excluded from participation. Thus, the study appears to have been enriched in participants with class 2 and class 3 obesity (BMI 35-39 and BMI ≥ 40), but diabetes, which is increasingly prevalent at these high BMI levels, was excluded, limiting the generalizability of the findings to an important subset of patients. The AHI decreased substantially with tirzepatide *vs*. placebo both among the participants using and not using PAP, by 23.8 and 20.0 events per hour, and body weight (adjusted for placebo) decreased 17.3% and 16.1% in the two groups, respectively. As incretin-based treatments lead to less weight loss among people with type 2 diabetes[2], exclusion of this group may have led to greater weight loss in patients randomized to tirzepatide in the study, although leaving us without an answer as to the role of tirzepatide in this highly important subset of patients. A systematic review and meta-analysis which examined glucagon-like peptide-1 receptor agonist (GLP-1 RA) efficacy in patients with diabetes reported that GLP-1 RAs reduced AHI by ~6 events per hour[3].

Department of Medicine, Division of Endocrinology, Diabetes and Bone Disease, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA.

Correspondence to: Prof. Zachary T. Bloomgarden, Department of Medicine, Division of Endocrinology, Diabetes and Bone Disease, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA. E-mail: zbloom@gmail.com

The authors endeavor to separately analyze (A) the effects of weight loss; (B) the effects of improvement in OSA markers; (C) direct effects of tirzepatide; and (D) interactions of (A), (B), and (C) as the underlying mechanisms explaining improvement in the following cardiometabolic factors (CMF): high-sensitivity C-reactive protein (hsCRP), high-density lipoprotein (HDL) and non-high-density lipoprotein (non-HDL) cholesterol, triglyceride, fasting insulin, homeostatic model assessment of insulin resistance (HOMA-IR), and systolic and diastolic blood pressure. The authors use a statistical approach termed "mediation analysis" to estimate these associations, while acknowledging that this approach is based on the statistical creation of "non-observable counterfactual scenarios." In other words, the paper can be seen as an exercise in the assessment of separate and combined effects of (A), (B), and (C) on CMF.

What did the authors report? They acknowledge that (A), (B), (C), and (D) are not cleanly distinguishable in the ordinary mechanistic sense. Weight loss affects OSA; OSA physiology may affect weight, appetite, inflammation, insulin resistance, and sympathetic tone; tirzepatide may affect cardiovascular (CV) risk through appetite, adiposity, glucose/insulin biology, renal/salt handling, inflammation, and sleep metrics simultaneously. So the "direct effect" (C) is statistically not being considered to act "through the mediators included and modeled," with the mediation analysis best seen as a statistical exercise which "compared the effect…through weight and OSA severity without reflecting on a possible direct effect of tirzepatide"[1].

The result of the mediation analysis was that for HOMA-IR, non-HDL and HDL cholesterol and triglyceride, and hsCRP, the combined effect of weight loss and improvement in OSA parameters beyond the "direct effect" of tirzepatide is greater than that of either alone, with improvement in OSA parameters appearing to have a lesser effect than weight loss. None of these parameters affected diastolic blood pressure beyond the effect of tirzepatide, and improvement in OSA parameters did not affect systolic blood pressure beyond the effect of tirzepatide, although an effect of weight loss was seen.

One must realize that the analysis includes biologically untestable assumptions. We know that weight loss and, based on the original study publication[4], improvement in OSA are strongly associated with tirzepatide treatment, calling into question the assumption of the statistical analysis that "direct" and "indirect" effects can be separated. As there is extensive evidence from studies of other incretin-based treatments that all agents in the class lower the CMF studied, it is unclear that the present study adds to the original publication, which concluded, "Among persons with moderate-to-severe obstructive sleep apnea and obesity, tirzepatide reduced the AHI, body weight, hypoxic burden, hsCRP concentration, and systolic blood pressure and improved sleep-related patient-reported outcomes[4]".

Finally, let us return to the question asked in the title of this commentary: Do we now know the effect on cardiometabolic outcome? Although the study focused on well-recognized CMF showing strong associations with outcome, the question of actual effects of tirzepatide on cardiovascular disease (CVD) events in people not having diabetes has not yet been addressed. The head-to-head trial of tirzepatide against dulaglutide in people with diabetes (excluded from the present study) showed the two to have similar reductions in events, although with trends suggesting that tirzepatide might be superior[5]. Among people not having a history of diabetes, only semaglutide has been shown to be associated with reduction in the combined endpoint of CV death, myocardial infarction or stroke in adults with BMI ≥ 27 and preexisting CVD[6]. Results of similar studies with tirzepatide are in progress[7] and will be of great importance.

DECLARATIONS

Authors' contributions

The author contributed solely to the article.

Availability of data and materials

Not applicable.

AI and AI-assisted tools statement

During the preparation of this manuscript, the AI tool ChatGPT (version GPT-5.6 Thinking, released 2026-07-09) was used to assist with literature organization and language editing. The tool did not influence the study design, data collection, analysis, interpretation, or scientific content of the work. All authors take full responsibility for the accuracy, integrity, and final content of the manuscript.

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Not applicable.

Consent for publication

Not applicable.

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