The need to address the risk of osteosarcopenia induced by tirzepatide therapy

Sirs,

The results of the SURMOUNT-1 trial showed that tirzepatide, a glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist, was able to induce weight loss in the range of -15.0% to -20.9%, depending on the administered dose, at 72 weeks (1), and more recently, the Investigators reported that tirzepatide therapy was safe and efficacious at lowering progression to type 2 diabetes after three years (2). Although patients may benefit from an effective anti-obesity treatment, there is a well-known causal relationship between significant weight loss and negative effects on bone mineral density (BMD) due to decreased mechanical loading (3). Tirzepatide was shown to enhance osteoclast number and decrease osteoblast number per bone area but did not affect bone mass in murine models over a period of four weeks (4). However, the literature lacks large human studies or *post-hoc* analyses on tirzepatide therapy assessing bone parameters (5). Moreover, the extent of weight loss induced by tirzepatide is more pronounced than that induced by semaglutide (4, 6) and may be closer to that resulting from bariatric surgery. Therefore, information regarding bone health, *e.g.* fracture incidence, BMD changes at lumbar spine, total hip and femoral neck, and/or changes in radial stiffness and failure load detected by high-resolution peripheral quantitative computed tomography (HR-pQCT) scans, would be of paramount importance. We suggest that future studies take this aspect into consideration so that, after the effects of tirzepatide on bone health have been ascertained in humans, appropriate preventive strategies could be adopted. Indeed, since a single infusion of zoledronic acid administered prior to bariatric surgery was shown to be significantly able to increase spine BMD and preserve hip BMD (7), it would be interesting to assess whether this approach might be effective also prior to prescription of tirzepatide.

Because tirzepatide can induce pronounced weight loss over a short time span, another key aspect to consider is the extent of loss of lean mass (LM), *i.e.* the proportion of fat-free mass (FFM) consisting of skeletal muscle (8). Although fat mass (FM) reduction improves general health, an uncontrolled LM loss may result in sarcopenia, a condition associated with impaired physical function, cognitive impairment, increased risk of falls, cardiovascular comorbidities, and high all-cause mortality (9). The effects of tirzepatide on LM have been unknown (8) until recently, when a *post-hoc* analysis (10) of the SURMOUNT-1 trial showed that treated individuals lost 10.9% of their LM on total body dual-energy x-ray absorptiometry (DXA) at 72 weeks, as compared to 2.6% observed in the placebo group. Out of total body weight reduction, the proportions of LM loss and FM loss (26% and 74%, respectively) (10) were in accordance with the recommended 'Quarter FFM Rule' (11) and showed similar effects to those observed with placebo (25% and 75%, respectively) and traditional anti-obesity strategies (10). However, a limitation to be aware of when interpreting these results is that the post-hoc analysis did not consider the dietary habits and extent of physical activity of the involved participants, and whether – or how – these correlated to DXA findings (10). Since the study subjects received professional nutritional consultations and physical training advice, perhaps a mitigation of LM loss resulting from underlying lifestyle optimisation cannot be excluded. Therefore, despite the favourable performance shown by tirzepatide in the aforementioned *post-hoc* analysis (10) as compared, for instance, to semaglutide (11, 12), it is nevertheless recommended to ensure that patients taking tirzepatide adopt proper strategies to avoid a disproportionate LM loss, such as resistance exercise and an increased protein intake (1.2–1.5 g/kg body weight/day, with 2–3 g of leucine per meal) (9).

In conclusion, while incretin-mimetic drugs such as tirzepatide have acquired popularity due to their potent anti-obesity action, their prescription requires that patients be adequately informed of possible effects on both BMD and LM loss in order to lower the risk of developing osteosarcopenia. A basic and simple preventive strategy is to ensure that patients perform resistance and balance exercises at least twice weekly, and to recommend an adequate intake of calcium, vitamin D, and protein. Close follow-up is necessary with DXA and muscle functional tests. Denosumab, an anti-receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor, has been suggested to have positive effects on both BMD and skeletal muscle (13), but real-word studies are needed to ascertain whether it could be a valid therapeutic option in patients at risk of osteosarcopenia under tirzepatide treatment.

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