Response to Letter to the Editor ¨*Menopausal hormone therapy is associated with reduced and total visceral adiposity, the OsteoLaus cohort*¨

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RESPONSE TO LETTER TO THE EDITOR:

We thank Dr Turner and Pr. Kerber for their interest in our article on the association between menopausal hormone therapy (MHT) and reduced android and visceral adiposity [1]. Their letter brings additional insight to the results of our study, providing important data from animal studies, which corroborate our findings and suggest underlying pathophysiological mechanisms.

In our article, we considered the benefits of MHT to derive from the direct effect of estrogen on adipose tissue, given the absence of significant differences between groups regarding potential intermediary factors such as caloric intake and physical activity. Nevertheless, as acknowledged in the article's discussion, the assessment of confounding factors was only partial, thus preventing us from drawing definitive conclusions. In their letter, Turner et al. highlight an elegant study in ovariectomized rodents, which revealed that 17β-estradiol supplementation restored normal lipolytic function, in contrast to physical exercise alone [2]. These data imply that MHT in our study may have reduced android fat and visceral adipose tissue via alteration of basic lipolytic rate.

The authors attribute the absence of residual effect in past users to the eventual down-regulation of estrogen receptor (ER) and subsequent loss-of-function of important estrogen-associated metabolic pathways. Though this speculation remains plausible, we would like to stress that the response of the target organs following MHT withdrawal seems to be tissue-specific, given our previous findings of a less pronounced rebound effect on bone density and microarchitecture [3].

Based on several animal studies, Turner et al. support the theory of 'euestrogenemia' [4] arguing in favor of the *critical window hypothesis* to explain that the estrogen receptor has distinct responses according to the timing of estrogen administration. Extrapolating these data to humans, we would expect that early MHT use would have more favorable outcomes, as suggested by subgroup analysis of the Women's Health Initiative [5]. More recently, the most convincing clinical data in favor of this hypothesis come from the ELITE randomized clinical trial (RCT), which showed reduced carotid-artery intima-media thickness after 6 months of MHT selectively in early (< 6 years) compared with late post-menopausal (> 10 years)

women [6]. In OsteoLaus, however, we were able to detect a benefit for BMI, android fat and VAT despite a broader age of studied population (50-80 years). A possible explanation is that MHT duration was relatively long (12.2 ± 8.8 years) for a mean age of 62.6 ± 6.7 years in current users. It is likely that MHT was started early after menopause in the majority of the participants, who fulfilled, thus, the criteria of 'eustrogenemia'.

In the light of the aforementioned evidence, we agree with Turner et al that the findings of our observational study should encourage further research to explore the optimal use of MHT.

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