Gender Differences in the Leptin Reduction Associated with Chronic Ketamine Use

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Background
Chronic and heavy use of ketamine, an NMDA (*N*-methyl-D-aspartate) antagonist which is widely used as a dissociative anesthetic, is associated with risks of addiction (Cheng et al., 2018, Chen et al., 2020). Ketamine dependence (KD) posts a threat to public health over past two decades in many countries. Because of its significant association with physical and psychiatric consequences such as depression and anxiety, leptin has been found to be linked with emotional disturbances and addiction. However, the role of leptin in ketamine addiction is not clear.

Aims & Objectives
To examine the differences of blood leptin levels between patients with KD and healthy controls, and to follow the alterations of levels after 1- and 2-week of ketamine discontinuation.

Methods
We enrolled 68 patients with KD and 62 controls. The serum levels of leptin were measured at baseline, 1 week, and 2 weeks after ketamine discontinuation. In addition, patients with KD were assessed by Beck Depression Inventory, Beck Anxiety Inventory, and Visual Analogue Scale for ketamine craving at baseline.

Results
KD patients had significantly lower serum leptin levels compared to the controls (3.7 ± 3.9 vs. 6.9 ± 6.3 ng/mL, $p < 0.001$). Furthermore, after stratified by sex, we found female patients had significantly lower levels of serum leptin at baseline compared to controls (4.7 ± 4.5 vs. 11.0 ± 7.2 ng/mL, $p = 0.002$), but the case-control differences were not seen in male patients (3.4 ± 3.6 vs. 4.2 ± 3.6 ng/mL, $p = 0.074$). Body mass index (BMI) was the only variable associated with leptin levels after adjustment. Also, the leptin levels significantly increased after 1- (3.6 ± 2.8, $p = 0.023$) and 2-week (3.8 ± 2.5, $p = 0.009$) of ketamine discontinuation.

Discussion & Conclusion
Chronic ketamine exposure is associated with leptin downregulation, which could increase after ketamine discontinuation. The attenuation of leptin reduction was observed in particular in female patients. The results may be explained by the augmentative effect of estrogen and upregulated estrogen receptors.