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EDITED BY
Xiang'En Shi,
Capital Medical University, China

REVIEWED BY
Cem Sulu,
Istanbul University Cerrahpasa, Türkiye
Dario De Alcubierre,
Sapienza University of Rome, Italy

*CORRESPONDENCE
Lukas Andereggen
lukas.andereggen@ksa.ch

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Commentary: Clinical characteristics of male prolactinoma patients mainly presenting with severe obesity and the metabolic response to dopamine agonist therapy

Lukas Andereggen [1,2]* and Emanuel Christ [3]

[1]Department of Neurosurgery, Kantonsspital Aarau, Aarau, Switzerland, [2]Faculty of Medicine, University of Bern, Bern, Switzerland, [3]Department of Endocrinology, Diabetology and Metabolism, University Hospital of Basel, Basel, Switzerland

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A Commentary on

Clinical characteristics of male prolactinoma patients mainly presenting with severe obesity and the metabolic response to dopamine agonist therapy

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We read with great interest the article by Wang et al. (1) reporting the characteristics of four men with prolactinoma and severe obesity (body mass index, BMI, range: 37.9-55.9 kg/m^2). Most men exhibited clinical signs of hypogonadism and presented with an adenoma ≤10mm.

After mean follow-up period of 36 ± 21 months, treatment with dopamine agonists (DAs) resulted in the control of prolactin (PRL) levels (baseline range: 72.3-273 µg/L; long-term range: 10.8-30.9). The median longitudinal change in BMI values (median ΔBMI/year) was -0.91 kg/^{2}/year (interquartile range (IQR) of -6.11 to -0.69). Alongside, improvements in metabolic profiles were observed.

The authors' conclude that DAs could potentially explain the weight loss alongside the metabolic advantages observed, stressing the importance of specifically screening prolactin (PRL) levels in men dealing with severe obesity.

The association between hyperprolactinemia and metabolic syndrome suggests that PRL itself acts as a regulator of body weight (2), with improvement in both BMI and metabolic profile credited to DAs therapy (3–5). In particular, individuals with prolactinoma exhibit higher BMI values and an increased incidence of obesity compared to the general population or even patients with non-functioning pituitary adenomas (6). The patients described in the cohort by Wang et al. (1) were exclusively men, aligning with the finding that males with prolactinoma exhibit higher BMIs compared to the general population (7). However, the

tumor diameter in their cohort was surprisingly small. Typically, macroprolactinoma patients tend to have higher BMI values compared to patients with microprolactinomas (8). This suggests that men, experiencing more subtle nonspecific symptoms – in addition to the supposed gradual weight gain- suffer from long-term exposure to high PRL levels in contrast to women who often present with amenorrhea, an easier-to-recognize symptom prompting timely investigation and intervention (9).

The potential role of PRL in the context of obesity and metabolic syndrome becomes apparent from the lack of significant weight loss observed upon treating non-functioning adenomas, unlike it has been observed in patients with prolactinomas (6). Interestingly, a study noted significant weight loss in macroprolactinomas but not in microprolactinomas (10). Additionally, anatomical extension of large prolactinomas toward the third ventricle may cause hypothalamic compression, potentially contributing to an increased BMI rather than being solely attributed to the direct effect of hyperprolactinemia, an observation although rare in adenomas, is a well-recognized occurrence, for example, in craniopharyngiomas (11, 12). Furthermore, hypogonadism itself with subsequent reduced testosterone levels, might be linked to decreased energy levels and diminished physical activity, thus contributing to weight gain (13).

In a recent comparative study of prolactinoma patients treated either with transsphenoidal surgery (TSS) or with DAs as the primary treatment option, we observed that normalizing PRL levels led to an improvement in patients' BMI. Notably, a significant reduction in weight was seen in the TSS cohort and a tendency for a BMI reduction in the DAs cohort (14). Considering that we noted no significant differences in the PRL levels in the long-term, it might be justified to infer that the speculated metabolic effect is likely attributable not solely to DAs themselves, but rather to the control of hyperprolactinemia and possibly the associated hypogonadism.

Considering the reported adenoma sizes in the Wang cohort, where the majority of patients have adenomas ≤10mm and are likely not infiltrating the cavernous sinus—though speculative, and noting that, at the last follow-up, all patients were still on DAs (1),—interdisciplinary discussions about upfront surgery in this specific cohort might at least be discussed, rather than committing to long-term DA therapy (9, 14–19). Whether TSS in prolactinoma patients is superior to standard care as a first-line or second-line treatment needs further investigation, particularly in an exclusive cohort of patients presenting with morbid obesity. In particular, we would like to emphasize that the primary goal is not about favoring TSS over DAs, but about controlling PRL with any means necessary to achieve a positive effect on the metabolic syndrome and BMI. Namely, in addition to managing hyperprolactinemia through surgical intervention, DA therapy, or a combination thereof, we emphasize the broader utility of DAs beyond prolactinomas (20). They have demonstrated efficacy in conditions such as Cushing's disease and acromegaly, wherein they contribute to the reduction of cortisol and IGF-1 levels, potentially facilitating metabolic improvements (21–24). Furthermore, it is crucial to underscore the significance of considering the effects of DAs on diabetes regulation and hypertension control independently of hormonal levels (25–27). Namely, it has been shown that increased D2RS protein expression in subcutaneous adipose tissue during hyperglycemia and T2D, coupled with dopamine receptor agonists' inhibition of adipocyte beta-adrenergic stimulation of lipolysis, may explain the observed positive effects on lipid metabolism in patients treated with bromocriptine (28). This comprehensive understanding enhances our insight into the metabolic alterations experienced by patients undergoing DA treatment.

To summarize, alongside recommending screening for PRL levels in severe obesity patients, we stress the importance of long-term correction of hyperprolactinemia and its linked hypogonadism. This might justify considering a primary surgical treatment approach as an alternative to DAs. Additionally, implementing programs for early control of weight loss interventions in this specific group of patients is crucial due to the potential high morbidity.

Acknowledging the unique and vulnerable nature of this cohort of prolactinoma patients, we commend Wang and colleagues for their insightful publication and detailed exploration of the impact of DAs on men with morbid obesity and prolactinoma. We encourage further studies to delve into the yet unexplored relationship between obesity and hyperprolactinemia, focusing on their long-term response to therapy.

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Conflict of interest

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