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Correspondence

Reply: Low bone mineral density is a common feature of Zellweger spectrum disorders

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Dear Editor,

We appreciated the thoughtful critique that was written by Poll-The and colleagues [1] regarding our manuscript on the bone health of patients with Zellweger spectrum disorders [2] (ZSD). They are indeed correct that many patients with Zellweger spectrum disorder are treated for adrenal insufficiency and that this steroid treatment could also influence bone mineral density. However, we would like to underscore the point that, in the case of systemic glucocorticoids, the poison is in the dose. Our patients were treated for primary adrenal insufficiency with physiologic doses of hydrocortisone that were carefully titrated to prevent signs and symptoms of adrenal insufficiency, while avoiding effects of steroid-induced Cushings. Over- or undersuppression of ACTH was also a biochemical metric used in the titration of glucocorticoids in this patient population. This resulted in a median dose of hydrocortisone of 13 mg/m^2 (range 7.8–23.1 mg/m^2) for the nine patients in our cohort who were treated with hydrocortisone.

What appears to be suggested by Poll-The and colleagues is that the decreased bone mineral density in patients with ZSD is in large part a reflection of glucocorticoid-induced osteoporosis (GIO). While we agree that this is important to delve more deeply into, we do not feel that GIO is the primary etiology for the decreased bone mineral density in our patients. The diagnosis of GIO is increasingly common in the pediatric population as these medications become more commonly used for rheumatologic diseases, renal diseases such as nephrotic disease, and asthma. The unifying feature of treatment for these disorders is that all generally require higher doses of therapy. As an example, a recent comprehensive study looked at the epidemiology of GIO in pediatric patients in Canada and found that the median initial glucocorticoid exposure was equivalent to 0.94 mg/kg of prednisolone equivalent [3]. By contrast, using the same measurements our patients are receiving a median glucocorticoid exposure equivalent to 0.13 mg/kg of prednisolone, which is nearly an order of magnitude lower.

Our cohort included nine patients who were treated with hydrocortisone and four patients who were not treated with hydrocortisone. Unfortunately, this small data set gives limited ability to provide high quality data analysis. We did find that the patients who did not receive steroid replacement had a lower median lumbar spine *Z*-score ($Z = -4.2$) as compared to patients who were treated ($Z = -2.9$), although this was not statistically significant ($p = 0.31$). Likewise, there were no differences observed between patients who were on treatment for adrenal insufficiency and those who were not treated for serum osteocalcin ($p = 0.65$) or serum CTX ($p = 0.32$).

Although we agree that discussion of adrenal insufficiency in ZSD is relevant for metabolic bone disease, the effects of physiologic replacement of glucocorticoids for adrenal insufficiency are qualitatively different from larger doses used for anti-inflammatory effect. The data we presented in our manuscript [2] support a primary etiology for bone disease in ZSD related to the underlying biochemical abnormalities of disease.

Competing interests

The authors declare that they have no competing interests related to this work.

Abbbreviations

ZSD	Zellweger spectrum disorder
GIO	glucocorticoid-induced osteoporosis
CTX	beta-crosslinked *c*-telopeptides

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