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EDITORIAL

Skeletal fragility induced by overtreatment of adrenal insufficiency

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It is well-known that both endogenous (such as in Cushing's syndrome) and exogenous (such as treatments with glucocorticoids, e.g., in inflammatory disorders) excessive glucocorticoid exposure can have detrimental effects on bones with decreased bone mineral density (BMD) and ultimately osteoporosis related fractures. However, the effects on bone health with replacement doses are more unclear.

Glucocorticoids affect the bone health in multiple ways [1]. Glucocorticoids lead to osteopenia and osteoporosis by suppressing bone formation via inhibiting osteoblast differentiation and function in addition to inhibiting intestinal vitamin D dependent calcium absorption. Moreover, glucocorticoids may also have indirect effects on bone health through derangements in neuroendocrine signals such as on growth hormone and insulin-like growth factor 1 (IGF-1) [1–3]. In fact both cortisol insufficiency and excess may impair growth hormone secretion [1]. However, endogenous glucocorticoids at physiological concentrations are needed for mesenchymal cell differentiation and normal bone development.

Studies on BMD in Addison's disease (AD) and congenital adrenal hyperplasia (CAH) are conflicting even though the majority of them seem to show decreased BMD [1, 4, 5]. So far the number of studies on fractures in patients on glucocorticoid and mineralocorticoid replacement therapy has been very limited [2, 3, 6–8]. An article published in this issue of *Endocrine* by Camozzi et al adds some important data on glucocorticoid and mineralocorticoid replacement on bone health [9]. They report on 87 patients with AD (median age 44 years, postmenopausal $n = 25$, menopause before age 40 $n = 7$) and compared them with 81 age- and sex-matched controls. Bone metabolism markers and dual-energy X-ray absorptiometry (DXA) were measured. Moreover, in those with a clear vertebral image on the DXA (61 patients with AD and 47 healthy controls) morphometric investigations to identify vertebral fractures were performed and assessed using Genant's classification. In patients with AD 31% ($n = 19$, five patients had multiple vertebral fractures) had at least one morphometric vertebral fracture compared to 13% ($n = 6$, none had multiple vertebral fractures) in controls, equivalent to an odds ratio of 3.1 (95% confidence interval 1.1–8.5). Unfortunately they did not report if any of these were symptomatic or if any other fractures were present in the patients' medical histories.

Surprisingly Camozzi et al. found no significant difference in BMD between patients and controls [9]. However, the absolute numbers in g/cm^2, *T*-scores and *Z*-scores in both lumbar spine and femoral neck were lower in individuals with AD indicating that if more patients and controls had been included a significant difference may have appeared. Furthermore, crush fractures will falsely increase BMD and it is unclear if this was accounted for. Thus, in reality the median BMD in lumbar spine may have been more decreased in those with vertebral fractures than reported and the BMD difference between the groups may have been significant. It is, however, previously known that using BMD as a predictor of future fractures in individuals exposed to glucocorticoid excess is unreliable [1], with BMD underestimating the fracture risk.

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Camozzi et al. also attempted to evaluate the glucocorticoid replacement by measuring 24 h urinary cortisol secretion which was non-significantly elevated in patients and significantly positively correlated with urine calcium excretion [9]. Unfortunately, we as treating physicians have a tendency to give supraphysiological glucocorticoid doses to minimize the risk of adrenal crisis in AD and CAH, but also to suppress adrenal androgens in the latter [4, 10, 11]. However, from a 2-year prospective study it was recently reported that a reduction of the glucocorticoid doses in AD and CAH led to improved BMD without increased risk of adrenal crisis while dose increments decreased BMD [12]. Also the formulations of oral glucocorticoids normally used cannot imitate the physiological circadian rhythm of cortisol secretion [5]. This can result in several high plasma cortisol peaks saturating the cortisol-biding globulin leading to high free cortisol concentrations at the tissue level. Lately modified release hydrocortisone preparations have been introduced better mimicking the diurnal rhythm [1], but if these have better effects on BMD and fracture risk have to be evaluated, preferably in randomized controlled trials.

Another interesting finding in the study by Camozzi et al. was that mineralocorticoid replacement was associated with better BMD [9]. It has been shown that the mineralocorticoid receptors are expressed in osteoblasts and osteoclasts although their functions are unclear. Moreover, mineralocorticoids have been used to minimize the glucocorticoid doses required in CAH [5], also occasional in non-classic CAH [13]. In fact individuals with CAH with less mineralocorticoid deficiency seem to have less fractures than those with the more severe forms of CAH [13]. Furthermore, BMD has been shown to positively correlate with fludrocortisone dose [3].

On the other hand, individuals with non-classic CAH are diagnosed later than those with classic forms and thus may have had more androgen exposure. This probably also have a positive effect on BMD. In contrast, in AD adrenal androgens are always low which may negatively affect bone health. Women with AD treated with the adrenal androgen dehydroepiandorsterone (DHEA) had better BMD and also less spontaneous vertebral fractures, even though the latter did not reach significance [8]. Yet, in a study of adult women with CAH there were no significant correlations between BMD and serum androgens concentrations, however, 44% had testosterone concentrations below detection limit [2].

Until we have more and larger studies, preferably randomized controlled trials, in this complex area a pragmatic view could be that all adult patients on low-dose glucocorticoid replacement therapy should have BMD monitored regularly, e.g., every 2–5 years, and previous fractures and type should be noted together with how they had occurred [5]. With the study by Camozzi et al. [9] assessing vertebral fractures using morphometric analysis of the vertebral images on the DXA could be added to these recommendations. Osteopenia, osteoporosis and low-trauma fractures should be handled as generally recommended but optimizing the glucocorticoid (and may be also formulation) and mineralocorticoid doses are important. Most likely more could be done to keep the androgen and estrogen concentrations within the reference range for the age and sex. However, these recommendations are not yet in any formal international guidelines.

Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interest.

Ethical approval This editorial does not report on original studies with human participants or animals performed by the author.

References

1. G. Mazziotti, A.M. Formenti, S. Frara, E. Roca, P. Mortini, A. Berruti, A. Giustina, Management of endocrine disease: risk of overtreatment in patients with adrenal insufficiency: current and emerging aspects. Eur. J. Endocrinol. **177**(5), R231–R248 (2017). https://doi.org/10.1530/EJE-17-0154
2. H. Falhammar, H. Filipsson, G. Holmdahl, P.O. Janson, A. Nordenskjold, K. Hagenfeldt, M. Thoren, Fractures and bone mineral density in adult women with 21-hydroxylase deficiency. J. Clin. Endocrinol. Metab. **92**(12), 4643–4649 (2007). https://doi.org/10.1210/jc.2007-0744
3. H. Falhammar, H. Filipsson Nystrom, A. Wedell, K. Brismar, M. Thoren, Bone mineral density, bone markers, and fractures in adult males with congenital adrenal hyperplasia. Eur. J. Endocrinol. **168**(3), 331–341 (2013). https://doi.org/10.1530/EJE-12-0865
4. P.W. Speiser, R. Azziz, L.S. Baskin, L. Ghizzoni, T.W. Hensle, D.P. Merke, H.F. Meyer-Bahlburg, W.L. Miller, V.M. Montori, S. E. Oberfield, M. Ritzen, P.C. White, Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society clinical practice guideline. J. Clin. Endocrinol. Metab. **95** (9), 4133–4160 (2010). https://doi.org/10.1210/jc.2009-2631
5. H. Falhammar, M. Thoren, Clinical outcomes in the management of congenital adrenal hyperplasia. Endocrine **41**(3), 355–373 (2012). https://doi.org/10.1007/s12020-011-9591-x
6. S. Bjornsdottir, M. Saaf, S. Bensing, O. Kampe, K. Michaelsson, J.F. Ludvigsson, Risk of hip fracture in Addison's disease: a population-based cohort study. J. Intern. Med. **270**(2), 187–195 (2011). https://doi.org/10.1111/j.1365-2796.2011.02352.x
7. K. Lovas, C.G. Gjesdal, M. Christensen, A.B. Wolff, B. Almas, J. Svartberg, K.J. Fougner, U. Syversen, J. Bollerslev, J.A. Falch, P. J. Hunt, V.K. Chatterjee, E.S. Husebye, Glucocorticoid replacement therapy and pharmacogenetics in Addison's disease: effects on bone. Eur. J. Endocrinol. **160**(6), 993–1002 (2009). https://doi.org/10.1530/EJE-08-0880
8. K.R. Koetz, M. Ventz, S. Diederich, M. Quinkler, Bone mineral density is not significantly reduced in adult patients on low-dose glucocorticoid replacement therapy. J. Clin. Endocrinol. Metab. **97**(1), 85–92 (2012). doi:jc.2011-2036 [pii] 10.1210/jc.2011-2036
9. V. Camozzi, C. Betterle, A. C. Frigo, V. Zaccariotto, M. Zaninotto, E. De Caneva, P. Lucato, W. Gomiero, S. Garelli, C.

Sabbadin, M. Salva, M. D. Costa, M. Boscaro, G. Luisetto, Vertebral fractures assessed with dual-energy X-ray absorptiometry in patients with Addison's disease on glucocorticoid and mineralocorticoid replacement therapy. Endocrine. (2017). https://doi.org/10.1007/s12020-017-1380-8

10. R.L. Rushworth, D.J. Torpy, H. Falhammar, Adrenal crises: perspectives and research directions. Endocrine **55**(2), 336–345 (2017). https://doi.org/10.1007/s12020-016-1204-2
11. S.R. Bornstein, B. Allolio, W. Arlt, A. Barthel, A. Don-Wauchope, G.D. Hammer, E.S. Husebye, D.P. Merke, M.H. Murad, C. A. Stratakis, D.J. Torpy, Diagnosis and treatment of primary adrenal insufficiency: an endocrine society clinical practice guideline. J. Clin. Endocrinol. Metab. **101**(2), 364–389 (2016). https://doi.org/10.1210/jc.2015-1710
12. J. Schulz, K.R. Frey, M.S. Cooper, K. Zopf, M. Ventz, S. Diederich, M. Quinkler, Reduction in daily hydrocortisone dose improves bone health in primary adrenal insufficiency. Eur. J. Endocrinol. **174**(4), 531–538 (2016). https://doi.org/10.1530/EJE-15-1096
13. H. Falhammar, A. Nordenstrom, Nonclassic congenital adrenal hyperplasia due to 21-hydroxylase deficiency: clinical presentation, diagnosis, treatment, and outcome. Endocrine **50**(1), 32–50 (2015). https://doi.org/10.1007/s12020-015-0656-0