Bilateral Femoral Head Avascular Necrosis with Physiological Doses of Steroids

Sir,

Avascular necrosis (AVN) of the femoral head is a dreaded complication of corticosteroid therapy. It can be seen in 3–40% of patients receiving corticosteroid therapy. In most cases, it is a result of high doses of steroids given for a long period of time, and usually such doses are used for anti-inflammatory, immunosuppressive or chemotherapeutic effect. Seldom is this complication seen in endocrinology practice because the usual doses used in endocrinology are physiological doses given as replacement for steroid deficiency. The glucocorticoids disturb various bone remodeling pathways, as well as cause inhibition of angiogenesis, coagulation abnormalities and so on making the bone prone to ischemia and poor recovery thereafter, making it susceptible to AVN.[1]

Recently we reported a case of bilateral femoral head AVN with replacement doses of oral prednisolone therapy.[2] This patient was a 38-year-old male with non-secreting pituitary macroadenoma who was operated and eventually developed pan-hypopituitarism for which he was treated with thyroxine, testosterone injections and replacement doses of corticosteroids. He had also received dexamethasone tablets 2 mg per day for 1 month prior to surgery. He presented 2 months after surgery with adrenal insufficiency when he was initiated on prednisolone 7.5 mg which was later reduced to a daily dose of 5 mg. After about 2 years of prednisolone therapy (daily dose 5 mg), he started having pain in bilateral hip associated with limping. He was diagnosed as bilateral femoral head AVN [Figure 1].

The second case we came across was a 60-year-old female patient who was diagnosed as Sheehan's syndrome at the age of 45 years. She had been on thyroxine and 5 mg of prednisolone for past 16 years (during which period she maintained a weight of 49–50 kg). Increase of prednisolone dose to 7.5 mg for 1 month during illness resulted in puffiness, fullness and redness of cheeks. She was subsequently shifted to hydrocortisone 20 mg daily, which she took for one-and-half years, after which she started experiencing pain in both hips in succession associated with progressing limping. She was evaluated for hip pain and found to be having AVN of both the femoral heads [Figure 2]. Her cortisol remained persistently low at 7.69 nmol/L, 12.6 nmol/L and 13.8 nmol/L during follow up. She could not tolerate further lowering of hydrocortisone doses.

In a meta-analysis of 22 studies, it was found that there is a 4.6-fold increase in incidence of AVN with every 10 mg/day increase in prednisone therapy in the first 6 months of corticosteroids therapy.[3] Felson *et al.* also noted a significant mean linear trend of higher daily prednisolone dose with development of osteonecrosis.[3] The first patient developed AVN while on prednisolone dose of around 5 mg (equivalent to 20 mg hydrocortisone) and the second patient developed AVN on 20 mg hydrocortisone. The usual replacement dose for adrenal insufficiency is 15–25 mg of hydrocortisone. Both hydrocortisone and prednisolone can

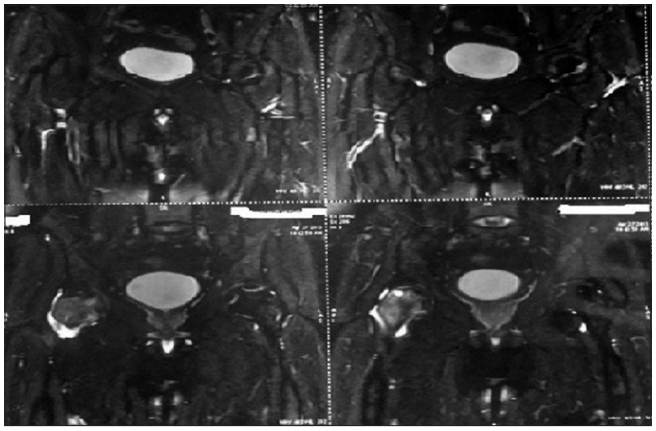

Figure 1: MRI of bilateral hip showing avascular necrosis of the femoral heads with the right side affected more than the left side

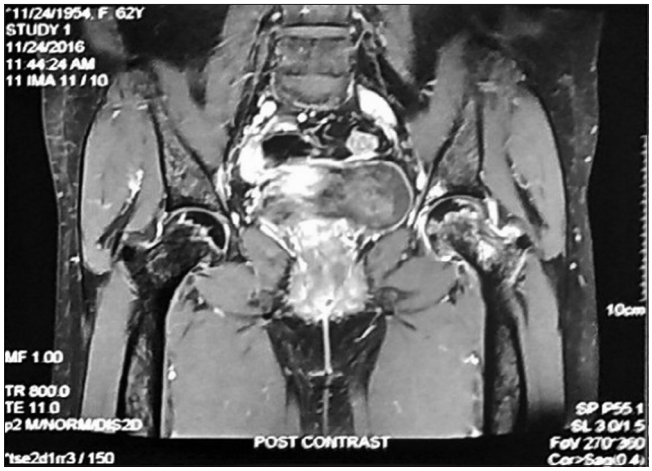

Figure 2: MRI hip showing avascular necrosis of both the femoral heads. Her serum cortisol remained persistently low (7.69 nmol/L; 12.6 nmol/L and 13.8 nmol/L). Because of mild redness of the cheeks an attempt to reduce prednisolone from 5 mg daily to 5 mg/2.5 mg on alternate days was made. However, it had to be increased again to 5 mg daily. Continued on same dose of steroids for another 2 years and it was subsequently changed to tab. Hisone 10 mg BD. Again an attempt was made to reduce the dose of steroids but patient did not tolerate

be given for replacement for steroid deficiency, however, prednisolone being cheaper and easily available is used by many physicians in India. In the first case, the patient had received dexamethasone for 1 month in the perioperative period along with the replacement doses given thereafter; however, AVN occurred 2 years later while on physiological doses. The second patient was always on physiological doses of steroids of prednisolone and hydrocortisone; and was never given any other more potent steroid.

A majority of studies have shown increased risk of AVN in patients receiving daily prednisolone dose of <20 mg. To the best of our knowledge, only two cases of steroid-induced osteonecrosis with lower doses have been reported earlier. Spencer *et al*.[4] reported femoral head AVN after 10 years of oral prednisolone doses of 4 mg per day; however, this patient had received high doses of prednisolone (100 mg/day; duration not specified) as well as intravenous methyl-prednisolone injections (dose not specified), previously. Williams and Corbett[5] reported two cases of hypopituitarism who were on replacement doses of steroids, one of them at a dose of prednisolone 7.5 mg reduced later to 5 mg for 2 years and the other received cortisol 5–10 mg per day for 14 months, before being diagnosed as AVN.

While replacement with steroids are required by all patients with primary and secondary adrenal insufficiency, it is intriguing how only a miniscule fraction develop AVN with such small doses of steroids and others do not. In a study done on rabbits it was found that low levels of steroid metabolizing hepatic activity may increase responsiveness to steroids and further increase risk of steroid-induced osteonecrosis even with low dose of steroid.[6] It is interesting to note that our second patient developed cushingoid features while on 7.5 mg prednisolone which had to be reduced to 5 mg subsequently. It is possible that steroid metabolising hepatic activity in an individual may affect the tissue responsiveness to even low doses of steroids.

These two cases highlight an important point that even low doses of corticosteroids can cause dreaded adverse effects and hence they should be actively looked for whenever there is slightest of suspicion. It is difficult to say whether short exposure to dexamethasone in the first case prior to prednisolone therapy or a long duration of steroids in the second case (prednisolone for 16 years and hydrocortisone for one-and-a-half years) may have contributed to AVN. It would be worthwhile to shift such patients to more physiological and less potent steroids like hydrocortisone as early as possible and whenever feasible.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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