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Differential skeletal recovery after surgical versus medical remission in Cushing's disease: a 5-year observational study

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BACKGROUND

Skeletal fragility is a major and often irreversible complication of Cushing's disease (CD). Although remission of hypercortisolism may allow partial bone recovery, long-term data comparing surgical and medical remission are scarce. In particular, whether sustained eucortisolism achieved through medical therapy results in skeletal recovery comparable to surgical cure remains unresolved.

METHODS

We conducted a 5-year retro-prospective observational study including 58 patients with CD and sustained normalization of 24-h urinary free cortisol (UFC), achieved after transsphenoidal surgery (surgical remission, n=36) or during long-term medical therapy (medical remission, n=22). Baseline assessment was performed during active disease. Endocrine, metabolic and skeletal evaluations, including DXA-derived bone mineral density (BMD) and fragility fracture assessment, were performed at 2 and 5 years after first UFC normalization. A complete 5-year follow-up was available in 33 patients (22 surgical, 11 medical).

RESULTS

At baseline, patients were comparable for age and biochemical severity, whereas disease duration before UFC normalization was significantly longer in medically treated patients (12 vs 1 months, p=0.001). Lumbar spine BMD significantly increased in the overall cohort at 2 years (0.863 vs 0.830 g/cm², p=0.018) and further at 5 years (0.960 vs 0.830 g/cm², p=0.001). This improvement was robust and consistent in surgically cured patients at both 2 (p=0.039) and 5 years (p=0.002), while only a non-significant trend was observed in the medical remission group. No significant changes were detected at femoral neck or total hip in either group.

The prevalence of densitometric osteoporosis decreased from 68% at baseline to 57% at 5 years. Despite biochemical remission, incident fragility fractures occurred during follow-up (3 at 2 years and 3 at 5 years). In multivariate regression analysis adjusted for age, sex, disease duration and baseline UFC, baseline lumbar spine BMD emerged as the only independent predictor of 5-year lumbar spine BMD (β=0.573, p=0.002).

BMD DURING FOLLOW-UP

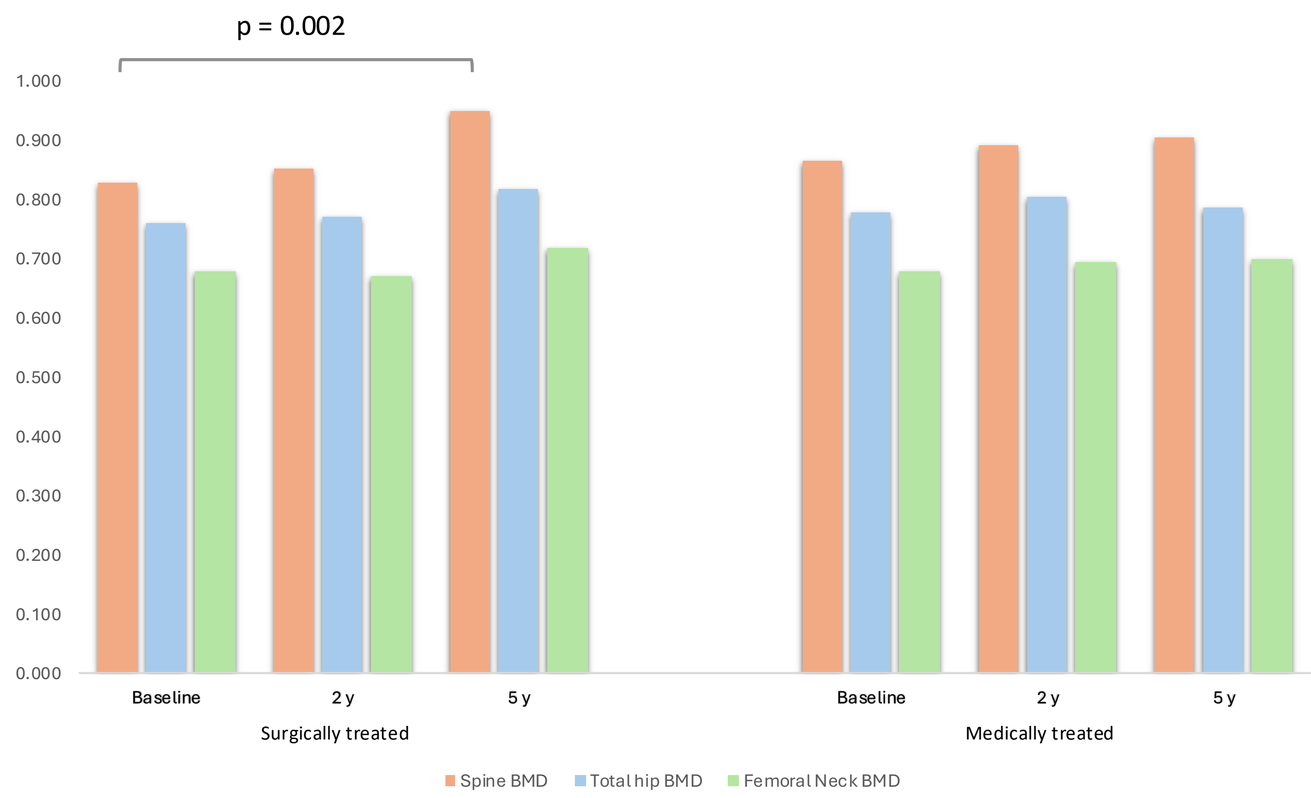


Figure 1. BMD during surgical and medical remission. Displayed p value: lumbar spine BMD at 5 years versus baseline in the surgical group.

MULTIVARIATE REGRESSION

Variable	Standardized β	p
Age	−0.261	0.142
Disease duration	−0.200	0.267
Baseline spine BMD	0.631	0.001
Sex	0.139	0.415
Baseline UFC	0.126	0.468

R^2 = 0.521; adjusted R^2 = 0.394; overall p = 0.01.

Table 1

Parameter	Surgery: baseline	Surgery: 5 years	Medical: baseline	Medical: 5 years
Lumbar spine BMD (g/cm²)	0.830 (0.180)	0.950 (0.260)*	0.865 (0.213)	0.905 (0.290)
Total hip BMD (g/cm²)	0.760 (0.192)	0.820 (0.124)	0.780 (0.190)	0.786 (0.324)
Femoral neck BMD (g/cm²)	0.680 (0.138)	0.719 (0.170)	0.680 (0.250)	0.701 (0.289)
25(OH)D (nmol/L)	54 (51)	80 (51)†	44 (44.8)	71 (37)‡
CTX (ng/L)	361.5 (522.5)	332 (416)	418 (305.3)	383 (254)§
bALP (µg/L)	13.3 (2.6)	13.2 (16.7)	15.6 (19.2)	13.4 (11.6)

Median (IQR). Versus baseline: *p=0.002; †p=0.029; ‡p=0.018. §Between-group comparison at 5 years: p=0.014. Other comparisons for these parameters were not significant.

CONCLUSIONS

In Cushing's disease, long-term skeletal recovery remains incomplete and strongly site-specific, predominantly affecting trabecular bone. Surgical remission is associated with a significantly greater lumbar spine BMD recovery compared with medical remission, despite sustained UFC normalization in both groups. Persistent fracture occurrence indicates that biochemical control alone does not fully restore skeletal integrity. Early diagnosis and baseline bone status critically determine long-term bone outcomes, supporting the need for prolonged skeletal surveillance and targeted bone-protective strategies, particularly in patients managed with long-term medical therapy.