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Weight Trajectory as a Predictor of Cushing's Disease

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Cushing's syndrome, a disorder of cortisol excess, is associated with significant morbidity and mortality. Obesity, hypertension and glucose intolerance are common clinical findings in patients with Cushing's, but with the increasing incidence of obesity worldwide—nearly 40% of the world's adult population is currently overweight—and the increasing incidence of obesity-associated comorbidities of hypertension and diabetes mellitus, deciding whom to screen for Cushing's can be very challenging and frequently delays timely diagnosis. We performed a retrospective study in patients with Cushing's disease (CD) and those with a clinically non-functioning ACTH-staining adenoma (NF-ACTH+) who underwent endoscopic endonasal resection at a large academic health center from 1/2015-7/2021 to investigate whether there are differences in weight-gain trajectories that can help differentiate patients with Cushing's from those without, even in a population that is predominantly

overweight-obese. We hypothesized that patients with Cushing's would have significantly greater increases in weight in the six months preceding surgery compared to NF-ACTH+ patients with similar pre-operative evaluation and similar pre-operative BMI. Patients with CD (n=50) were younger (mean±SD: 45.9±15.4 years) compared to patients with NF-ACTH+ (n=34) (54.2±15.1 years, p=0.02) and a higher percentage were female (CD: 86% versus NF-ACTH+: 50%, p=0.0003). CD and NF-ACTH+ patients were of similar BMI (CD: 34.5±9.2 kg/m² and NF-ACTH+: 33.8±6.7 kg/m², p=0.93), even after controlling for age and sex (p=0.47), and >90% of both CD and NF-ACTH+ had a BMI of >25 kg/m². Median weight change in the six months prior to surgery was 2.5 [0.3, 5.4] kg in CD and -0.5 [-2.7, 1.6] kg in NF-ACTH+ (p<0.02); 77% of CD versus 43% of NF-ACTH+ gained weight during the six-month period (p=0.02). Using a minimally clinically significant weight gain of 2kg, 56.4% of CD versus 21.4% of NF-ACTH+ gained >2kg in the six months preceding surgery (p=0.02); using a 3kg cut off, 46% of CD versus only 14.3% of NF-ACTH+ gained >3kg in the six months preceding surgery (p=0.03). After controlling for use of insulin in the setting of diabetes mellitus, the results remained significant with more CD patients than NF-ACTH+ gaining >2kg or >3kg in the six months prior to surgery (p<0.04 for both analyses). These data demonstrate that patients with Cushing's are significantly more likely to gain at least 2kg (4.4 lbs) over a six-month period compared to a similarly overweight/obese population without clinical Cushing's, independent of the use of insulin in the setting of diabetes mellitus. A weight increase of at least 2kg can potentially allow weight to continue to be used as a helpful sign of Cushing's despite the increasing incidence of obesity. Collectively, these data suggest value in using weight trajectories, rather than absolute BMI, as a clinical variable when assessing the pretest probability of Cushing's.

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