Growth Hormone Releasing Hormone Reduces Plasma Markers of Immune Activation and Hepatic Immune Pathways in Nonalcoholic Fatty Liver Disease

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Introduction: The GH/IGF-1 axis affects multiple metabolic pathways, and animal models demonstrate that it also modulates immune function. Little is known, however, regarding effects of augmenting GH secretion on immune function in humans. This study used proteomics and gene set enrichment analysis to assess effects of a GH releasing hormone (GHRH) analog, tesamorelin, on circulating immune markers and immune-related gene pathways in the liver in people with HIV (PWH) and NAFLD. We hypothesized that tesamorelin would decrease circulating markers of immune activation in conjunction with previously reported reductions in visceral fat and hepatic triglyceride. **Methods:** 92 biomarkers associated with immune function (Olink Immuno-Oncology panel) were measured in plasma samples from 61 PWH with NAFLD who participated in a double-blind, randomized, 12-month trial of tesamorelin versus identical placebo. Proteins differentially altered by tesamorelin at a false discovery rate < 0.1 were considered significantly changed. Gene set enrichment analysis targeted to immune pathways was subsequently performed on liver tissue from serial biopsies. **Results:** Compared to placebo, tesamorelin decreased circulating concentrations of 13 proteins, including four chemokines (C-C Motif Chemokine Ligands 3 [CCL3, effect size -0.38 Log_2 fold change], 4 [CCL4, -0.36 Log_2 fold change], and 13 [CCL13 or MCP4, -0.42 Log_2 fold change] and interleukin-8 [-0.50 Log_2 fold change]), two cytokines (interleukin-10 [-0.32 Log_2 fold change] and cytokine stimulating factor 1 [-0.22 Log_2 fold change]), and four T-cell associated molecules (CD8A [-0.37 Log_2 fold change], Cytotoxic And Regulatory T Cell Molecule [CRTAM, -0.47 Log_2 fold change], granzyme A [-0.53 Log_2 fold change], and adhesion G protein-coupled receptor G1 [ADGRG1, -0.54 Log_2 fold change]), as well as arginase-1 [-0.95 Log_2 fold change], galectin-9 [-0.26 Log_2 fold change], and hepatocyte growth factor [-0.30 Log_2 fold change]. No proteins in the panel were significantly increased by tesamorelin. Network analysis indicated close interaction among the gene pathways responsible for the reduced proteins, with imputational analyses suggesting down regulation of a closely related cluster of immune pathways. Targeted transcriptomics using tissue from liver biopsy confirmed an end-organ signal of down-regulated immune pathways, including pathways involved in antigen presentation, complement activation, toll like receptor and inflammatory signaling, and T-cell activation. **Conclusions:** Long-term treatment with tesamorelin decreased circulating markers of T-cell and monocyte/macrophage activity, with corresponding downregulation of immune pathways in the liver. These findings suggest that augmenting pulsatile GH may ameliorate immune activation in a population with metabolic dysregulation and systemic inflammation.

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Long-Term Corticotroph Function Following Cure of Cushing's Syndrome

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Introduction: Hyper- and hypofunction of the hypothalamic-pituitary-adrenal (HPA) axis in Cushing's syndrome (CS) and Addison's disease (AD) is associated with disturbances of classical feedback mechanisms. Time to recovery of adrenal function after CS remission depends on the etiology of CS and is longest after adrenal CS. To date there are no data on the recovery of corticotroph function following CS remission, and the synacthen test is recommended for testing adrenal function in patients with hypopituitarism. **Aim** Here we aim to test corticotroph function after long-term cure of Cushing's syndrome following bilateral adrenalectomy (BADx), compared to patients with primary glucocorticoid deficiency due the presence of 21-hydroxylase antibodies or adrenoleucodystrophy, a pathophysiological model of glucocorticoid and mineralocorticoid deficiency. **Methods:** We retrospectively evaluated data from patients with CS and AD attending our endocrine department between 2000 and 2020, using the following inclusion criteria: BADx performed for pituitary/ectopic/adrenal or occult CS or primary adrenal insufficiency confirmed either by the presence of 21-hydroxylase antibodies or genetically in adrenoleucodystrophy. **Results:** Full data were available for 93 patients: 43 patients with BADx due to CS (18 patients with pituitary CS, 14 patients with adrenal CS and 11 patients with ectopic/occult CS, F:M 29:14, mean age at BADx 45.4 years age range 13-74 years) and 50 patients with AD (47 cases with positive 21-hydroxylase antibodies, 3 cases with adrenoleucodystrophy, F:M ratio 27:23, mean age at diagnosis 35 years, age range 6-57 years). The observation period was 537.5 patient-years after BADx (mean 12.5 years, range 1-38 years) and 647 patient-years following AD diagnosis (mean 14.2 years, range 1-46 years). At the last visit, there were no differences between the hormone substitution regimes between the groups. ACTH concentrations during the whole observation period and also at the last visit were lowest in patients with adrenal CS (56.5 pg/ml) when compared to patients with AD (487 pg/ml, $p<0.001$), or with patients with pituitary CS (377.5 pg/mL, $p=0.011$). ACTH values in patients with AD in long-term follow-up were significantly higher when compared to all patients with CS (141 pg/mL, $p<0.001$). **Conclusion:**

These data highlight a long-term defective corticotroph function in patients with CS following BADx. Low ACTH concentrations long term after BADx for adrenal CS corroborate that corticotroph function fails to recover after CS cure. In the light of these findings, the utility of the synacthen test for excluding secondary/tertiary adrenal insufficiency following CS remission is disputable and remains to be evaluated in future studies dedicated to CS cohorts.

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Longitudinal Study of Prevalence of Sodium Abnormalities in Hospitalized Patients With COVID-19

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Background: Sodium abnormalities (dysnatremia) are frequently observed in patients with community-acquired pneumonia and are associated with excess mortality. Data on the prevalence of hyponatremia and hypernatremia (serum sodium [Na] < 135 and > 145 mmol/L respectively) in patients with coronavirus disease 19 (COVID-19) are currently lacking. **Methods:** The aim of this study was to evaluate the prevalence and etiology of hyponatremia and hypernatremia at several timepoints during hospitalization of COVID-19 patients. This retrospective, longitudinal, observational study included all COVID-19 positive adult patients admitted to two London hospitals over an 8-week period (February to May 2020). **Results:** Clinic records were reviewed in 488 patients, 277 males (56.8%) and 211 females (43.2%), with a median age of 68 years. Comorbidities were documented in 79.6%, with the commonest being hypertension (45.7%), diabetes mellitus (25%), and chronic kidney disease (16.4%). Prior to admission, 25 patients (5.1%) had pre-existing chronic hyponatremia. At hospital presentation, median [Na] concentration was 137 mmol/L. Dysnatremia was present in 146 patients (29.9%), including 26 (5.3%) with hypernatremia and 120 (24.6%) with hyponatremia, of whom [Na] was 130-134 mmol/L in 90 (18.4%) and < 130 mmol/L in 30 (6.2%). Only 19% of patients with < 130 mmol/L underwent adequate laboratory assessment of the etiology of hyponatremia. Of those, based on a urinary sodium cut-off of 30 mmol/L, hyponatremia was classified as hypovolemia in 75% and non-hypovolemic in 25%. For the remaining hyponatremic cases, using 5 mmol/L as the cut-off value for plasma urea, 55.7% were classified as probable hypovolemic and 44.3% non-hypovolemic hyponatremia. There was an upward trajectory of [Na] values during hospital stay with a median increase of 2 mmol/L in the first 48 hours following admission. On the fifth day of hospitalization, the prevalence was similar for hypernatremia and hyponatremia (13.8% and 14.1%, respectively). On the tenth day, hypernatremia was more common than hyponatremia (14.2% vs 10.2% respectively). Analysis of [Na] throughout the hospital stay defined four subgroups; 185 patients (37.9%) remained normonatremic throughout hospitalization; 180 (36.9%) had exposure to hyponatremia; 53 (10.9%) were exposed to hypernatremia; and 70 (14.3%) experienced both hypernatremia and hyponatremia. **Conclusions:** Hyponatremia, usually mild, was common at admission in Covid-19 positive patients, while hypovolemic hyponatremia appeared to be the predominant etiology. During hospital stay, abnormal sodium concentration was recorded in more than two thirds of Covid-19 positive patients. The association of dysnatremia with the outcomes in hospitalized COVID-19 patients warrants further exploration.

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Olfactory Performance in Youth With Full and Subthreshold Avoidant/Restrictive Food Intake Disorder

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Background: Avoidant/restrictive (A/R) food intake disorder (ARFID) is characterized by restrictive eating defined by lack of interest in food, sensory sensitivity, and/or fear of aversive consequences of eating resulting in a failure to meet adequate nutritional and/or energy needs. The complex psychopathology that differentiates ARFID from other eating disorders highlights the need to explore the role of sensory systems in disease etiology. Olfaction has an important role in eating behavior. Specifically, olfactory dysfunction is associated with decreased food intake and appetite. Olfactory performance and associated clinical characteristics have yet to be examined in individuals with ARFID. We hypothesized that higher levels of PYY, which signals satiety, would be associated with poorer olfactory performance; whereas greater food fussiness and A/R eating severity would be associated with stronger olfactory performance. **Methods:** We evaluated a cross-sectional sample of children and adolescents with full and subthreshold ARFID (n=82, 46.2% female, mean age 15.8±3.8). We measured olfactory performance with the Sniffin' Sticks test (Burghardt®, Wedel, Germany) which captures odor discrimination, odor identification, and odor threshold. Higher