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Objective: to evaluate metabolism of vitamin D and calcium-phosphorus metabolism in patients with an active phase of acromegaly in comparison with healthy individuals. **Materials and Methods:** The study included 44 patients with an active acromegaly (IGF-1 788 [521; 963] ng/mL), as well as 49 conditionally healthy individuals. There were more men in the Acromegaly group (41% vs. 20%, p <0.05), patients were older (median age 42.7 [35.5; 26.5] vs. 26.3 [25; 33.5] years, p <0.05) and had a higher BMI (28.4 [25.2; 30.2] vs. 22.2 [20.1; 26.1] kg/m2, p <0.05) in a minor way compared with the control group. All participants were tested for vitamin D metabolites (25(OH)D3, 25(OH) D2, 1,25(OH)2D3, 3-epi-25(OH)D3 and 24,25(OH)2D3) by UPLC-MS/MS, free 25(OH)D and vitamin D-binding protein by ELISA, PTH by electrochemiluminescence immunoassay, as well as routine biochemical parameters of blood serum (calcium, phosphorus, creatinine, albumin, magnesium) and urine (calcium and phosphorus-creatinine ratio in spot urine). **Results:** In the Acromegaly group, we observed significantly higher levels of serum total calcium (2.46 [2.37; 2.56] vs. 2.38 [2.33; 2.45] mmol/L, p <0.05), albumin-corrected calcium (2.33 [2.28; 2.42] vs. 2.26 [2.21; 2.31] mmol/L, p <0.05) and phosphorus (1.39 [1.25; 1.55] vs. 1.15 [1.06; 1.23] mmol/L, p <0.05) as well as lower levels of serum albumin (45 [44; 47] vs. 46 [45; 48] g/L, p <0.05). The rest of the studied biochemical parameters and PTH levels did not differ significantly between the groups. The IGF-1 level in patients with acromegaly positively correlated with the level of total calcium (r = 0.49, p <0.05), albumin-corrected calcium (r = 0.49, p <0.05) and phosphorus (r = 0.55, p <0.05). The Acromegaly group showed lower levels of 25(OH)D3 (14.8 [11.8; 20.5] vs. 20.5 [14.8; 24.6] ng/mL, p <0.05), 3-epi-25(OH)D3 (1.0 [0.7; 1.4] vs. 1.4 [0.9; 1.8] ng/mL, p <0.05), 24,25(OH)2D3 (0.8 [0.4; 1.2] vs. 1.7 [0.9; 2.6] ng/ml, p <0.05) and free 25(OH)D (4.6 [3.7; 5.6] vs. 5.9 [4.0; 7.5] pg/mL, p <0.05), higher levels of 1,25(OH)2D3 (50 [42; 63] vs. 39 [34; 45] pg/mL, p <0.05), a lower 25(OH)D3/1,25(OH)2D3 ratio (289 [226; 443] vs. 517 [340; 641], p <0.05) and a higher 25(OH)D3/24,25(OH)2D3 ratio (19.3 [15.4; 27.7] vs. 11.9 [9.6; 15.2], p <0.05). Conclusion: Our data suggest that high levels of the active vitamin D metabolite (1,25(OH)2D3) resulting from an increase in 1α-hydroxylase activity may contribute to the elevation of calcium and phosphorus serum levels in patients with acromegaly. Our results also indicate a decrease in 24-hydroxylase activity in patients with acromegaly, which may be due to lower levels of 25(OH)D3 in these patients. The results obtained should be evaluated taking into account the observed differences in age, gender and BMI between groups.

Neuroendocrinology and Pituitary
TOOLS AND MECHANISMS OF REGULATION IN THE ANTERIOR PITUITARY

Novel Pituitary Organoid Model as Powerful Tool to Unravel Pituitary Stem Cell Biology Across Ages and Disease

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The pituitary gland harbors a population of stem cells. However, role and regulation of these cells remain poorly understood. We recently established organoids from mouse pituitary as a novel research tool to explore pituitary stem cell biology (Cox et al., J. Endocrinol. 2019; 240:287-308). In general, organoids represent 3D *in vitro* cell configurations that develop and self-organize from (single) tissue stem cells under well-defined culture conditions that typically mirror the stem cell niche and/or embryogenic processes. Organoids reliably recapitulate key aspects of the original organ, including of its stem cell compartment. Moreover, organoids are long-term expandable while retaining these properties. We demonstrated that pituitary organoids originate from the resident ($SOX2^+$) stem cells, largely phenocopy these cells and retain the stemness phenotype during expansive culture. Interestingly, the organoids show confident *in vivo* translatability and, when developed from transgenically damaged gland, recapitulate the activation status of the stem cells as observed *in situ* following injury. Now, we found that the organoids also mirror the stem cells' phenotype and biology in physiological conditions in which the stem cell compartment is either activated or compromised. Organoids from the neonatal maturing pituitary reproduce phenotypical and functional aspects of its activated stem cells, whereas organoids from aging gland mimic the declined functional state of the stem cells in old pituitary. Interestingly, this functional decay was found to be reverted during organoid culture, indicating that the old pituitary stem cells retain intrinsic functionality but are *in vivo* restrained by an obstructive microenvironment, not present in the organoid culture. Indeed, using single-cell transcriptomics and *in vivo* analysis, we found that the aging pituitary suffers from a prevailing inflammatory state (inflammaging) which appears to raise the threshold for stem cell activation. Interestingly, comparison of young and old pituitary led us to the discovery of pituitary stem cell activators. Finally, we found that activated parameters of organoid formation are also observed when tumorigenesis takes place in the gland, again mimicking the *in situ* stem cell activation that is occurring in this perturbed, pathological condition. Taken together, we identified, and applied, our new pituitary organoid model as advanced and powerful tool to gain profound insight into pituitary stem cell behavior across life and disease, which is expected to eventually translate into restorative and rejuvenative tactics when pituitary function is compromised by damage or age. In this context, our single-cell transcriptome database has strong potential to unveil appealing targets.

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Pituitary Somatotroph Adenoma Cell-Derived Exosomes: Characterization of Novel Non-Hormonal Functions

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