Adipose Tissue, Appetite, and Obesity
INTEGRATED PHYSIOLOGY OF OBESITY AND METABOLIC DISEASE

The Relation Between Cortisol and Anthropometric Measurements Throughout Lifespan: A Systematic Review and Meta-Analysis

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Introduction: Recently, cross-sectional studies report associations between long-term glucocorticoid levels in scalp hair (HairGC) and obesity. However, there is a wide variation in studied outcomes and associations, possibly caused by differences in population characteristics, *e.g.* age, sex, dispersion of adiposity, and used laboratory methods. The aim of this systematic review and meta-analysis was to investigate the relation between HairGC and anthropometrics and to explore possible moderators of this association. **Methods:** We searched the Medline, Embase, Cochrane, Web of Science, Scopus, Cinahl, PsycInfo, and Google Scholar databases for articles that relate HairGC to measures of adiposity (date 11-16-2020). Primary outcomes were correlations between hair cortisol (HairF) and cortisone (HairE), and anthropometrics: BMI, waist circumference (WC) and waist-hip-ratio (WHR). Authors were contacted to provide missing outcome information. Pooled correlation coefficients were calculated using random effects models. Assessment of heterogeneity was performed using the I^2 statistic. Exploratory moderator analyses were performed with subgroup analyses and meta-regression. This systematic review was performed in accordance to the PRISMA guidelines. **Results:** Our systematic search identified 150 cohorts, comprising a total of 37,107 unique individuals, of which 15,033 sampled from population-based cohorts. For BMI, the pooled correlation for HairF was 0.121 (95% CI 0.083–0.158, n=26,941; I^2 94.2%, p<0.001) and for HairE 0.108 (95% CI 0.047–0.167, n=7,250; I^2 52%, p<0.01). For WC, the pooled correlation for HairF was 0.111 (95% CI 0.058–0.164, n=10,290; I^2 63%, p<0.01) and for HairE 0.200 (95% CI 0.137–0.264, n=2,198; I^2 0%, p=0.42). For WHR, the pooled correlation for HairF was 0.102 (95% CI 0.040–0.163, n=6,865; I^2 27%, p=0.14) and for HairE 0.261 (95% CI 0.195–0.330, n=1,314; I^2 0%, p=0.40). A higher percentage of male participants was related to stronger correlations with WC (p<0.001), but not with BMI and WHR. Mean age, mean BMI, and mean HairGC levels of the cohorts did not significantly moderate the pooled correlations, neither did the used laboratory techniques (immunoassays vs mass spectrometry-based assays).
Conclusion: This unique, large meta-analysis demonstrates that long-term endogenous glucocorticoids as assessed by HairGC show small but consistent correlations to measures of obesity, despite a large heterogeneity between the included cohorts. The strongest associations were found between HairE and WC and between HairE and WHR. This suggests that glucocorticoid levels in the high-normal range, especially cortisone, may contribute to or reflect the state of specifically central adiposity, even within the general population.

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Timing of Onset of Adverse Events With Setmelanotide, an MC4R Agonist, in Patients With Severe Obesity Due to LEPR or POMC Deficiency

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Introduction: Setmelanotide is a melanocortin 4 receptor agonist indicated for chronic weight management in patients with obesity due to proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency. This analysis aimed to assess the timing of the onset of adverse events (AEs) of special interest in patients with POMC/PCSK1 or LEPR deficiency obesity treated with setmelanotide. **Methods:** The timing of AE onset with setmelanotide was evaluated in a pooled set of patients with POMC/PCSK1 or LEPR deficiency who received setmelanotide in Phase 2 (RM-493-011 [NCT02507492]) or Phase 3 (RM-493-012 [NCT02896192] and RM-493-015 [NCT03287960]) clinical trials. Patients in the Phase 2 investigator-initiated trial (Charité Universitätsmedizin Berlin) received open-label setmelanotide for 12 to 13 weeks followed by an extension study for eligible patients. The Phase 3 trials included a 12-week open-label phase, an 8-week placebo-controlled phase, and a subsequent 32-week open-label phase, for a total treatment length of at least 1 year. AEs were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). AEs of special interest were defined as those related to treatment-emergent AEs (TEAEs) commonly occurring with setmelanotide (hyperpigmentation disorders, disturbances in sexual arousal, nausea, vomiting, injection site reactions [ISRs]). **Results:** As of November 10, 2020, 35 patients (15 POMC, 2 PCSK1, 18 LEPR) were enrolled and included across the 3 trials; 2 patients in the Phase 2 trial were ongoing treatment as of the cutoff. Daily setmelanotide dose ranged from 0.25 to 3.0 mg. All patients experienced ≥1 TEAE, the most common being skin hyperpigmentation (85.7%), injection site erythema (68.6%), nausea (57.1%), and headache (51.4%). For AEs of special interest, hyperpigmentation disorders occurred in 85.7% of patients (30/35), disturbances in sexual arousal in 17.1% (6/35), nausea in 57.1% (20/35), vomiting in 28.6% (10/35), and ISRs in 88.6% (31/35). The onset of most hyperpigmentation disorder (34/53 events; 64.2%) and disturbances in sexual arousal
(6/11 events; 54.6%) AEs were during Month 1 after starting setmelanotide. Onset of nausea and vomiting were most frequent during Month 1 of treatment (nausea: 12/34 events [35.3%]; vomiting: 6/19 events [31.6%]). ISRs occurred throughout the trial, with 41.6% (91/219 events)