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)

having an onset within Month 1 of treatment. Eighteen serious AEs occurred, none were interpreted as related to the study drug. **Conclusions:** In patients with POMC/PCSK1 or LEPR deficiency obesity who received setmelanotide treatment, the onset of AEs of special interest in any month was generally highest during Month 1 of treatment, with fewer events occurring during subsequent months. Apart from hyperpigmentation, all AEs occurred intermittently.

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Trends in the Racial and Ethnic Disparity and Predictors of Hepatic Steatosis: Data From NHANES III and NHANES 2017–2018

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Hepatic steatosis is a serious problem worldwide and it affects Hispanics at a higher rate than Blacks. This disparity is an important public health problem. The purpose of this study was to examine the trend in the racial/ethnic disparity of hepatic steatosis among a representative sample of the U.S. adult ≥20 years old in two time-periods. Data from the National Health and Nutrition Examination Survey (NHANES) III (1988–1994) and NHANES 2017–2018 were analyzed. The sample size in the two respective cycles was 13,910 and 5,492 respectively. Hepatic steatosis in NHANES III was diagnosed using ultrasound while in NHANES 2017–2018, fibroscan was used. We analyzed the data using bivariate Chi square, and multiple logistic regression to adjusting for confounding variables and considering the design and sample weights. In both time-periods, Mexican American had the highest prevalence of hepatic steatosis (28% in NHANES III and 43% in NHANES 2017–2018) compared to the other racial/ethnic groups ($p<0.05$). In the adjusted logistic regression model, relative to the white population, Mexican-Americans had 40% higher odds of hepatic steatosis in NHANES III (adjusted odds ratio [AOR]=1.4, 95% confidence level [CL]=1.1–1.9, $p<0.05$) and 200% higher odds of hepatic steatosis in NHANES 2017–2018 (AOR=2.0, 95% CL=1.3–3.1, $p<0.05$). The common predictors of hepatic steatosis in the two time periods were gender, high waist-to-hip ratio, borderline and high levels of triglyceride, and prediabetes and diabetes as diagnosed by HbA1c ($p<0.05$). For CRP, independent of the method used, mild and significant inflammation were predictors of hepatic steatosis ($p<0.05$). In NHANES 2017–2018, participants ≥ 65 years (compared to 20–34 years of age) and Blacks (relative to Whites) had a lower chance of hepatic steatosis in the adjusted regression model ($p<0.05$), and those inactive (relative to those who met the physical activity guideline) had a higher chance of hepatic steatosis ($p<0.05$). The increased prevalence of hepatic steatosis in 2017–2018 compared to 1988–1994, may be related to the obesity epidemic, although differences in methodological factors may also play a role. Our study indicated that the racial/ethnic disparity in hepatic steatosis especially among Mexican American persisted over time. Future work is needed to explore the persistence of the racial/ethnic disparity of hepatic steatosis and its underlying mechanisms.

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Weight Loss Mobile Apps: Do They Address COVID-19 and Diabetes

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Background: Over 70 million Americans are obese and 99 million are overweight. There are over 3.7 billion ehealth mobile app downloads per year. Weight loss apps offer information on exercise and nutrition as well as weight tracking. Obesity is a risk factor for COVID-19 infection, along with diabetes and hypertension. In addition, obesity plays a role in the increased mortality of COVID patients. In March of 2020, the U.S. government, through the Small Business Administration and through the Small Business Innovation Research program, as well as through Facebook and Google, offered individuals and companies money for public education and/or solutions for the COVID-19 epidemic. Thus, are software app developers adding information about COVID-19 for their audience? Specifically, do weight loss apps mention obesity being a risk factor for DM, Hypertension, and COVID-19? Weight loss apps target a young demographic, and for public health purposes, COVID-19 information needs to reach this demographic since obesity can be a risk factor for COVID-19 infection. **Purpose**: Do weight loss apps provide information about DM, HTN, and COVID-19 during this pandemic era? **Methods:** Evaluation of the 10 most popular apps in the Apple (iOS) and Google (Android) stores via the search term "weight loss." Apps were ranked by downloads/star rating respectively for Android and iOS apps. Apple does not provide information about the number of downloads. App inclusion criteria: 1) Free 2) iOS: star ratings greater than 4 (greater than 10K ratings); Android: greater than or equal to 1 Million downloads; App features: DM, HTN, Race, Gender, COVID-19, BMI, Heart Disease, Calorie Count, and Fitness. **Results:** DM: 0/20, HTN: 0/20, BMI: 19/20, while Race is 0/20; Gender 19/20; COVID-19: 0/20; Calorie Count 11/20; Fitness 13/20. **Conclusion**: 1) Weight Loss apps have not ventured in the public education realm of risk factors and comorbidities of COVID-19 despite the pandemic in 2020. 2) As physicians, we should continue to educate our patients with weight issues and other risk factors in the era of a worldwide pandemic.