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Platform Research Presentations: Health Impacts of Chronic Illness or Social Conditions on Adolescent Health

24.

DIFFERENTIAL EXPRESSION OF SALIVARY MICRORNA IN ANOREXIA NERVOSA AND ANXIETY DISORDERS

Anna M. Scipioni, BA, Rollyn M. Ornstein, MD, Steven D. Hicks, MD, PhD

Penn State College of Medicine

Purpose: Micro ribonucleic acids (miRNAs) regulate protein translation throughout the human body, influencing diverse processes such as brain development and metabolism. Brain to saliva transfer of miRNAs may occur through the cranial nerves, glymphatic drainage or perfusion of the salivary glands. They are altered in psychiatric conditions, such as depression, but have not been studied in anorexia nervosa (AN), a disorder with both psychiatric and metabolic features. The purpose of this study was to identify salivary miRNAs “altered” in AN that may offer diagnostic and therapeutic targets.

Methods: Participants were females, age 11-21 years, with: 1) restrictive-type AN, at the outset of partial hospitalization treatment; 2) anxiety (AX); and 3) healthy controls (HC). Morning pre- and post-prandial salivary samples were collected. RNA was quantified using high throughput sequencing. Partek Flow was used to align mature and premature miRNAs with the human genome. Significance analysis of microarray (SAM) identified individual miRNAs with differences between 20 AN, 20 AX and 18 HC samples. Variable importance projection (VIP) scores were used to quantify miRNA contributions to group separation on partial least squares discriminant analysis (PLSDA), and hierarchical clustering was used to visualize expression patterns across individual samples. Fasting and post-prandial miRNA levels were compared across AN and non-AN samples with 2-way analysis of variance (ANOVA). MiRNAs of interest were functionally interrogated in DIANA miRPath software. Relationships between miRNAs and medical/neuropsychiatric characteristics were investigated with Pearson correlation analyses.

Results: PLSDA and hierarchical clustering analyses revealed distinct distribution patterns for AN, AX and HC samples. Ten individual miRNAs had significant VIP scores (≥ 2.0) that were critical for group separation. 5 miRNAs were downregulated in both AN and AX, which may be anxiety related. 5 were upregulated in AN only, suggesting that these changes are related to malnutrition. MiRNAs upregulated in AN identified in DIANA miRPath showed enrichment (FDR < 0.05) for several KEGG pathways including fatty acid biosynthesis ($p=2.06E-19$, 2 miRNAs), fatty acid metabolism ($p=4.00E-07$, 8 miRNAs), regulation of pluripotency of stem cells ($p=3.83E-06$, 14 miRNAs), steroid hormone biosynthesis ($p=9.43E-06$, 8 miRNAs), biotin metabolism ($p=3.66E-05$, 2 miRNAs) and GABAergic signaling ($p=0.037232$, 13 miRNAs) pathways. Three miRNAs demonstrated a dynamic response to food intake by 2-way ANOVA Simultaneous Components Analysis (ASCA) of fasting and post-prandial samples in those with AN and those without AN. All 3 miRNAs tended to be lower in AN during the fasting state and higher in the post-prandial state. Individual miRNA levels were associated with both medical characteristics and neuropsychiatric measures.

Conclusions: Salivary miRNA profiles are disrupted in adolescent females with AN, demonstrating potential utility for differentiating adolescent females with AN from peers. These miRNAs are influenced by prandial-status, target genes related to fatty acid metabolism and GABAergic signaling, and are related to neuropsychiatric measures. They yield potential insights into the pathophysiologic milieu underlying AN and may provide an objective measure for tracking AN severity, or treatment response.

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25.

GLOBAL SALIVARY MICROBIOME ACTIVITY IN FEMALE ADOLESCENTS WITH ANOREXIA NERVOSA

Anna M. Scipioni, BA, Xiang Zhan, PhD, Steven D. Hicks, MD, PhD, Rollyn M. Ornstein, MD

Penn State College of Medicine

Purpose: Alterations in the gastrointestinal (GI) microbiome and gut-brain axis have been demonstrated in a range of neuropsychiatric disorders, likely through gene-environment interactions. Anorexia nervosa (AN) is a life-threatening mental illness with strong genetic underpinnings, and is characterized by dysregulated psychologic, metabolic and weight-regulation processes. The GI microbiome is implicated in many of these processes, affecting weight loss/gain, energy extraction from the diet, and communication with the brain via the gut-brain axis. The oropharynx represents the sole entry-point of the GI tract, lying in close proximity to the brain and cranial nerves. Evidence has shown that the microbial community residing in the oral cavity is a close representation of that in the upper GI tract, suggesting a role for the salivary microbiome as a diagnostic and prognostic tool for diseases affecting the GI tract. The oropharynx may represent a site of AN pathology, e.g. decreased taste sensation. Preliminary research suggests intestinal dysbiosis in AN, but the salivary microbiome has not been investigated.

Methods: We characterized the salivary microbiome of females (age 11-21 years) with AN restrictive-type at the outset of treatment, in comparison to healthy controls (HC) and patients with anxiety (AX), a common comorbid diagnosis. Morning pre- and post-prandial salivary samples, and AN post-treatment samples, were collected (n=70). RNA sequencing was used to compare differences in taxa activity (at multiple taxonomic ranks), as well as alpha diversity (within sample) and beta diversity (between sample) among AN, AX, and HC groups. For global analysis, microbiome activity differences between groups were evaluated via permutational analysis of variance (PERMANOVA). The Wilcoxon rank sum test was used to identify differential activity of each individual taxon between groups and across pre/post-treatment AN samples.

Results: There was a significant difference in the global microbiome activity between AN and HC groups ($p=0.004$) as reflected by both alpha-diversity and beta-diversity comparisons, indicating salivary dysbiosis in AN. Six genera showed significantly different abundances between AN and HC samples, four of which were more abundant in AN and two of which were less abundant in AN. *Rhodobacter*, a genus more abundant in AN, includes species which possess an extensive range of metabolic capabilities. *Leptospira*, also more abundant in AN, is a spirochete bacteria that causes generalized symptoms such as vomiting, jaundice, abdominal pain, and diarrhea. Individual taxa comparisons between AN and AX/HC identified 13 taxa which uniquely characterized AN microbial samples, including enrichment in Proteobacteria and depletion in Firmicutes. Pre- and post-treatment comparison demonstrated a shift in activity of these 13 taxa towards a healthier state after treatment.

Conclusions: This study presents evidence of upper GI microbiome dysbiosis in AN, consistent with previous gut microbiome findings. Several of the genera differentially expressed in AN are implicated in functional pathways that are characteristically dysregulated in the disease state of AN. Additionally, the salivary microbiome appears to improve to a healthier state following treatment. Future directions include uncovering the differential effects of nutrition/weight restoration and psychological improvement.

Sources of Support: Quadrant Biosciences, Inc. and the Brad Hollinger Eating Disorders Research Endowment

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26.

IMPACT OF ADRENAL AND GONADAL HORMONE SUPPLEMENTATION ON BONE GEOMETRY IN TEENS WITH ANOREXIA NERVOSA

Amy Desrochers DiVasta, MD, MMSc¹, Henry Feldman, PhD¹, Jennifer M. O'Donnell, BA², Catherine M. Gordon, MD, MSc¹

¹Boston Children's Hospital; ²Robert Wood Johnson Medical School

Purpose: Adolescents with anorexia nervosa (AN) may have reduced secretion of dehydroepiandrosterone (DHEA) and estrogen that contributes to skeletal deficits. We sought to determine whether DHEA + estrogen replacement therapy (ERT) prevented bone loss in young adolescent girls with AN.

Methods: We recruited females with AN (n=70), ages 11-18 years, from two hospital-based adolescent clinics into a 12-month, double-blind, placebo-controlled trial. Participants were randomized to receive either oral micronized DHEA 50 mg + 20 mcg ethinyl estradiol/0.1 mg levonorgestrel daily (n=35) or placebo (n=35). Main outcomes included measurements of bone mineral density (BMD) by dual-energy X-ray absorptiometry (DXA; total body, hip, lumbar spine) and peripheral quantitative computed tomography (pQCT; tibia) at baseline, 6 months, and 12 months. MRI T1-weighted images of the left knee + T1 relaxometry were obtained to determine physeal status. Biomarkers of bone turnover were measured. We analyzed each outcome using repeated-measures analysis of variance. Models were adjusted for age, baseline height and weight, menarchal status, duration of amenorrhea, and physeal status (open or at least partially closed).

Results: Sixty two subjects completed the trial. Physeal closure status was the strongest predictor of changes in aBMD. In participants with open physes at baseline, total body BMD-Z score decreased over 12 months in participants receiving DHEA+ERT (-0.9 ± 0.5 , $p=0.02$) and remained unchanged in placebo subjects (p difference=0.02). Similar declines in BMD Z-score over time DHEA+ERT were seen at the spine (-1.5 ± 0.5 , $p=0.01$) and hip (-0.5 ± 0.6 , $p=0.03$) in subjects receiving; no changes were observed for placebo subjects. In contrast, in participants with -closed physes, no changes in BMD Z-scores were detected at any site with DHEA+ERT or placebo (p difference >0.05 for all). Treatment did not affect any pQCT measures over the 12-month trial, regardless of physeal closure status. Bone formation markers responded most strongly in the DHEA+ERT group and those with open physes.

Conclusions: In young adolescents with AN and open physes, replacement of adrenal and gonadal hormones led to a decline in markers of bone health over 12 months of treatment. No benefit of treatment was seen in skeletal outcomes obtained at either the axial or appendicular skeleton. Physeal closure status was an important effect modifier of the impact of hormonal therapy on these bone outcomes. It appears that subjects with open physes at baseline showed decreases in aBMD and BMD Z-scores in response to this therapy. The data suggest that the previously demonstrated potential skeletal benefits derived from this therapy apply only to older adolescents and young women who have completed their growth and have closed epiphyses. Therefore, other therapeutic strategies would be recommended in young patients affected with this disease, in addition to standard multidisciplinary care including medical, nutritional, and psychological support.

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27.

'IT IS THIS WHICH IS NORMAL' A QUALITATIVE STUDY ON WOMEN'S EXPERIENCES WITH CHILD MARRIAGE AND HEALTH IN CONAKRY, GUINEA

Yvette Efevbera, M.Sc., D.Sc.

Harvard University TH Chan School of Public Health

Purpose: Child marriage, a union before age 18, has been associated with poor health behaviors and outcomes in quantitative literature, yet limited research qualitatively explores women's health experiences in child marriage. The purpose of this study was to investigate how women married as children in Conakry, Guinea, where more than 50% of women marry before age 18, perceive their health as related to their child marriages.

Methods: This qualitative study used grounded theory. A purposive sample of girls and women who married before age 18 participated in in-depth interviews (N=19). Interviews were conducted in French or a local language and ranged from 45 to 90 minutes. Open coding was used to categorize data and identify key themes. Informed consent was received from participants and ethical board approval was provided by the Harvard Longwood Institutional Review Board and Guinea's National Council for Health Research.

Results: Two overarching themes and nine sub-themes emerged. Participants described their perceptions of the negative health outcomes they experienced as related to their child marriages. Interviews revealed women perceived their mental health, sexual and reproductive health, and physical health were negatively impacted by their marriages. Participants also described their perceptions of health benefits they experienced as related to their child marriages. Benefits identified included good health, increased access to health care, and childbearing practices.

Conclusions: Understanding that women married before age 18 perceive both disadvantages and benefits to their health contributes to a narrative currently missing from literature. Research, practice, and policy addressing child marriage and women's health needs to intentionally incorporate the perspective of women impacted.

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28.

NO ASSOCIATION BETWEEN THE PREVALENCE OF HYPOVITAMINOSIS D AND THE OCCURRENCE OF FRACTURES AMONG OVERWEIGHT/OBESE ADOLESCENTS

Andrea Meisman, MA¹, Adi Ziv, MD¹, David Segal, MD², Andrea R. Meisman, MA¹, Jordan Fry, BS³, Mekibib Altaye, PHD¹, Catherine M. Gordon, MD, MS¹

¹Cincinnati Children's Hospital Medical Center; ²Meir Medical Center, Israel; ³The Ohio State University

Purpose: There are conflicting data regarding the association between fracture incidence and serum vitamin D (25OHD) concentrations among adolescents with respect to body mass index (BMI) and age. The current study explored the potential association between a low 25OHD level and fracture among overweight, obese, and morbidly obese adolescents.

Methods: A case-control study was conducted. We reviewed 1,129 electronic medical records of outpatients aged 12-19 years, who presented to the adolescent clinic of an urban hospital between October 1, 2014 – October 1, 2017 and for whom 25OHD levels were available. Patients were excluded if they had chronic diseases that could affect bone health and/or if they received medications that affected bone and mineral metabolism. Participants were identified as cases if they sustained a low/medium impact fracture 12 months before or after the 25OHD level was measured. Twenty-seven were identified [mean (SD) 3.56 (2.1) months between the fracture and 25OHD measurement], with 26 having their 25OHD level taken <6 months before or after the fracture. Controls were matched by age, race, BMI percentile and the season at which their 25OHD was measured (n=81). 25OHD status was defined as sufficient (>30 ng/mL), insufficient (20-30 ng/mL), and deficient (<20 ng/mL) in accordance with the Endocrine Society Clinical Practice Guidelines. Additionally, data were collected regarding fracture location and mechanism, season, hospitalization, and modality of treatment. Independent sample t-tests were used to evaluate for a difference in the 25OHD levels between the two groups. An alpha of 0.05 was considered statistically significant

Results: In total, 108 participants were included in the study. The case participants included 15 males (55.6%) and 12 females (44.4%). The control group was composed of 48 females (59.3%) and 33 males (40.7%). For all participants, the mean age was 15.7 ± 2.4 years. 12% were overweight, 53.7% were obese, and 34.3% were morbidly obese. Most fractures involved the upper extremity (59.3%) and were sustained by a low impact mechanism. The mean 25OHD level was 18.5 ng/mL for case participants and 16.1 ng/mL for control participants (P=0.1), indicating deficiency in both groups. No correlations were found between 25OHD levels and fractures, overall, or in any of the weight groups

Conclusions: While extremely low levels of 25OHD were common among the adolescents studied, the occurrence of a fracture did not imply lower 25OHD levels among overweight, obese and morbidly obese adolescents. These data suggest that this costly laboratory testing is not justified with respect to bone health prior to vitamin D supplementation

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29.

OPIOID USE AMONG JUVENILE JUSTICE-INVOLVED ADOLESCENTS

Allyson L. Dir, Ph.D., Matthew C. Aalsma, Ph.D., Sarah Wiehe, MD

Indiana University School of Medicine

Purpose: Substance use rates are high among juvenile justice-involved adolescents. Although recent research and policy efforts have sought to address opioid use among adult offenders, fewer efforts have targeted opioid use among adolescent offenders. The goal of the study was to examine prevalence of opioid use among juvenile justice-involved adolescents as well as rates of recidivism and participation in court-ordered substance use programs among opioid-using adolescents.

Methods: A retrospective cohort study was conducted among youth arrested between ages 8-18 years in Marion County, Indiana (Indianapolis metropolitan area) between November 2006 and April 2017. Electronic data were extracted from the Marion County Juvenile Justice System (MCJJS). Institutional Review Board approval was granted by Indiana University-Purdue University Indianapolis and by relevant review boards of the collaborating agencies. A sub-sample of 9,429 youth with complete data regarding court-ordered requirements and drug screen results were used for analyses (59% male; M(SD)age=15(1.92) at first arrest; 56.8% black). Individuals with any positive drug screen results for opioids were coded as opioid users. Individuals with positive drug screens for other drugs as well as individuals with negative drug screen results were also coded accordingly. Recidivism was defined as any new incident or arrest within two years following the individual's initial arrest (0=no recidivism, 1=recidivism). Preliminary analyses examined prevalence rates of opioid and other substance use in the sample. Chi-square analyses were conducted to rates of court-ordered assignment to substance use programs, rates of substance use program completion (0=did not complete, 1=complete), and recidivism.

Results: Of 9,429 youth, 5% (n=450) were identified as opioid users. Only 33.6% (n=150) of opioid users were ordered to complete a substance use program as part of their requirement. Of those, 60% (n=90) successfully completed the substance use program. Opioid users were also less likely to successfully complete court-ordered mental health programs compared to non substance users (64.4% vs. 74.9%; p=.01). Among all opioid users, 72.3% (n=337) recidivated within 2 years following their first arrest/charge; opioid users were significantly more likely to recidivate compared to non substance users (p<.01). Further, those who successfully completed substance use and mental health programs were also less likely to recidivate.

Conclusions: Despite the seemingly low rates of opioid use, results highlight that these adolescents are a particularly vulnerable group; even compared to other substance-using adolescents, opioid users are less likely to successfully complete substance use programs and are also at a higher risk of recidivism. Findings for low rates of individuals ordered to substance use programs despite the severity of their substance use is concerning and underscore the need for improved screening/assessment of substance use and other mental health problems by the juvenile justice system as well as consideration of substance use problems in case dispositions and assignment of individuals to court-ordered programs and other requirements. Further evaluation of substance use effectiveness is needed, including identifying barriers to individuals' engagement in programs and successful completion of programs.

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