# Cardiovascular Endocrinology

## HYPERTRIGLYCERIDEMIA; INFLAMMATION AND MUSCLE METABOLISM IN OBESITY AND WEIGHT LOSS II

### *Inflammasome Components After Bariatric Surgery: Novel Targets for a Chronic Disease*

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**SUN-540**

**Background**: Obesity is a metabolic chronic disease with important associated morbidity and mortality. Bariatric surgery (BS) is the most effective treatment for keeping long-term weight loss in severe obesity and consequently decreases obesity-related complications including inflammation. **Aim**: to explore changes in the inflammasome components after BS and their relations with clinical and biochemical parameters at baseline and six months after surgery. **Patients and methods:** 22 patients that underwent BS (sleeve gastrectomy and roux-en-Y gastric bypass) were included. Epidemiological, clinical, anthropometric and biochemical evaluation was performed. Four groups of inflammasome components and inflammatory associated factors were evaluated: NOD-like receptors; inflammasome activation components; cytoquines and inflammation/apoptosis related components; and cell-cycle and DNA-damage regulators. Clinical-molecular correlations and associations were for the first time performed in a cohort of patients with morbid obesity that underwent BS. **Results**: The four groups of inflammasome components were dysregulated after BS. The mRNA expression of several factors was markedly decreased after BS, specially CXCL3, CCL8, TLR4, NLRC4 and NLRP12. Most changes were independent of the performed surgical technique. Inflammasome components displayed several clinical and biochemical correlations including the presence of baseline metabolic comorbidities (type2 diabetes, dyslipidemia and hypetension) and the body composition. **Conclusion:** the regulation of several inflammasome system components may explain the improvement and reversion of some obesity-related comorbidities after BS.

# Genetics and Development (including Gene Regulation)

## GENETICS AND DEVELOPMENT AND NON-STEROID HORMONE SIGNALING II

### *Novel GLI2 Mutations Identified in Pediatric Patients with Combined Pituitary Hormone Deficiency: One Gene, Various Genotypes.*

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Combined pituitary hormone deficiency (CPHD) is an important clinical problem caused by mutations in more than 30 different genes. Six genes in the Sonic Hedgehog (SHH) signalling pathway are reported to cause CPHD. SHH signaling is essential to induce pituitary cell identity in cells of Rathke's pouch by stimulating expression of the transcription factors *Lhx3* and *Lhx4*. In the absence of SHH signaling, a repressive isoform of the transcription factor GLI2 (Gli-Kruppel family member 2) suppresses gene expression. In the presence of SHH signaling, the activating form of GLI2 gains access to the nucleus and induces expression of downstream target genes. Heterozygous GLI2 loss of function mutations are found in patients with holoprosencephaly (HPE), HPE-like phenotypes associated with pituitary anomalies, and combined pituitary hormone deficiency with or without other extra-pituitary findings. We sought to identify the cause of CPHD in 171 unrelated patients diagnosed with or without extra-pituitary manifestations that were recruited from several Argentinean medical centers. We conducted panel sequencing, and identified GLI2 heterozygous variants that were rare and predicted to be deleterious in two unrelated patients, (p.L761P and p.1404Lfs) and a single, heterozygous, rare, likely deleterious GLI2 variant identified by exome sequencing (p.A203T). p.L761P and p.A203T variants were previously reported as candidates for HPE/CPHD, no functional studies were carried out to determine the effect of the variants on the gene function. We performed functional analysis of these variants using a mammalian cell line (NIH/3T3-CG) previously engineered to be a sensor for SHH signaling. It was stably transfected with a reporter gene that expresses GFP in response to GLI2 activation by a SHH agonist. We modified this cell line to assay GLI2 variants. We created a homozygous knock out of both endogenous *Gli2* genes using CRISPR-Cas9 editing, and individual cell clones were selected for loss of GFP expression in response to SHH agonist treatment by FACS. We verified that transfecting the knockout cells with wild type *Gli2* restored SHH responsive GFP expression. We assayed the ability of three patient GLI2 variants to rescue GFP expression and SHH agonist responsiveness and found that all three failed to fully rescue to wild type levels. This supports the hypothesis that the GLI2 variants in three CPHD patients are likely pathogenic. Thus, we identified three likely pathogenic GLI2 mutations in CPHD patients

from Argentina. The variable phenotype of patients with GLI2 mutations worldwide could be caused by variation in other genes, environmental exposures, maternal effects, and/or epigenetic factors.

# Healthcare Delivery and Education

## EXPANDING CLINICAL CONSIDERATIONS FOR PATIENT TESTING AND CARE

### *Reducing Unnecessary Repeat HbA1c Testing in a Tertiary Academic Hospital*

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**MON-118**

Reducing Unnecessary Repeat HbA1c Testing in a Tertiary Academic Hospital.

Background

Glycated hemoglobin (HbA1c) is a surrogate marker of glycemia over the preceding three months, where the last 30 days contributes to 50% of the value (1). Therefore guidelines often recommend repeating HbA1c only after 3 months in most situations (2), but repeat testing of HbA1c is often conducted earlier when not warranted (3). We aimed to conduct a Quality Improvement (QI) initiative to reduce unnecessary repeat testing of HbA1c at a large tertiary care academic hospital in Toronto, Ontario by 50% by May 2020.

Methods:

The Model for Improvement Quality Improvement (QI) framework was used in the design of the QI project to reduce repeat HbA1c. Problem characterization was conducted to understand root causes and iterative Plan-Do-Study-Act cycles were used to develop a change intervention. Unnecessary HbA1c tests were the primary outcome and defined as repeat HbA1c testing within 60 days; the top three specialities that ordered unnecessary HbA1c tests were targeted for education prior to implementation of the change intervention.

Results:

Baseline data on all HbA1c tests in 2018 revealed repeat testing in approximately 10% of 15,290 HbA1c tests, with estimated potential savings of more than $11,000 based on the provincial reimbursement rate. The top 3 ordering specialities targeted for education included Nephrology (n=410 repeat HbA1c tests), Cardiology (n=246 repeat HbA1c tests), and Endocrinology (n=136 repeat HbA1C tests). Root cause analysis revealed that providers often ordered repeat HbA1c tests due to being unaware of prior results and a knowledge gap of testing recommendations. A laboratory forced function will be implemented on December 1, 2019 to cancel any repeat HbA1c tests within 60 days and calls to the lab to add HbA1c testing will be tracked.

Conclusions:

Repeat HbA1c testing is frequent in hospital settings and can be an important target for QI efforts. A forced function to cancel processing of repeat HbA1c may be an appropriate QI intervention to reduce repeat testing to promote high-value care. Ongoing data analysis will be conducted to assess the impact of this intervention.

References

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# Neuroendocrinology and Pituitary

## PITUITARY TUMORS II

### *Clinical Features in Patients with Hypercorticism*

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Clinical Features in Patients with Hypercorticism.

Cushing's disease is a severe multimorbid pathology affecting mainly people of young working age. In most cases, the diagnosis of the disease is acute and the patient is observed for a long time by doctors of different specialties with complications of hypercorticism.

Purpose: To identify the most frequent clinical manifestations of hypercorticism at the time of diagnosis of Cushing's disease, to analyze the relationship of clinical manifestations of hypercorticism with the main clinical and laboratory indicators.

Material and methods: 25 patients were examined, including 15 women and 10 men with Cushing's disease, registered in Samarkand Endocrinology Clinic.

Results: Majority of patients (68%) were in age 25-40, the average age was 37. The median duration of the disease was 35,5 months. Matronism, the most characteristic manifestation of hypercortisolism was observed in 36% (9 patients). This is most often associated with hypercorticism symptoms were striae and acne, which were found in 56% (14 patients), osteoporosis 40% (10). The most frequent complaints were weight gain, fatigue, headache, menstrual disturbances. A number of symptoms had a positive correlation with cortisol levels.

Conclusion: Clinical manifestations of hypercorticolism are mainly nonspecific. Striae and acne were found in high frequency. Therefore these key features, namely a change in facial appearance, weight gain, elevation of BMI and the presence of genital virilisation should alert the clinician to the possibility of Cushing's disease and initiate laboratory evaluation.