mice at 7 and 2 days prior to euthanasia to label bones. Decalcified tibiae were embedded in paraffin for histological analysis. Undecalcified tibiae were embedded in plastic for dynamic histomorphometry. Micro-computed tomography (μCT) was used to access bone microarchitecture of femurs and vertebrae followed by biomechanical testing of bone strength. The μCT data of distal femurs show that cPTH treatment increased bone volume in female KO mice (6.864 ± 2.318 vs 4.690 ± 1.555 %; P= 0.0328; n=9 per group) and maintained bone in male KO mice (13.37 ± 2.860 vs 13.38 ± 3.135; P= 0.9968, n= 10) compared to control. Histological analysis show higher osteoclastic activity in both sexes and genotypes when treated with cPTH, suggesting that the anabolic response may be at the level of osteoblasts and osteocytes. These promising results support our hypothesis that arrestin-mediated PTH receptor downregulation plays an importance role in bone weakness associated with hyperparathyroidism. These studies are important for understanding the clinical phenotype of PHPT patients and suggest that inhibition of β-arr2 in PHPT could be a path for drug therapy.

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Adipose Tissue, Appetite, and Obesity

RARE CAUSES AND CONDITIONS OF OBESITY: PRADER WILLI SYNDROME, LIPODYSTROPHY

Weight Loss After Glucagon-Like Peptide-1 Receptor Agonist Treatment in Childhood Obesity with Diabetes and Cirrhosis Associated with a Homozygous MC4R Mutation

Philippe Klee, MD-PhD, Mirjam Dirlewanger, MD, Valérie McLin, MD, Maria Teresa Carminho, MD, Valerie M. Schwitzgebel, MD.
University Hospitals of Geneva, Geneva, Switzerland.

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Background

Mutations in the melanocortin-4 receptor (MC4R) represent the most common cause of monogenic obesity. Treatment options are limited but glucagon-like peptide-1 receptor agonists (GLP-1 RA) may be of use to induce weight loss.

Methods

Exome of the patient was captured using the Agilent SureSelect QXT Human All Exon V5 kit and sequenced on Illumina.

Clinical findings and results

We report obesity-associated diabetes and cirrhosis in a 13-year girl born from consanguineous parents of Afghan origin. Past medical history revealed mild mental retardation and excessive weight gain since infancy. Linear growth was normal. Her father was obese and no diabetes was found in the family. The girl was initially investigated for hoarseness and found to have pulmonary hypertension, later accepted to be secondary to cirrhosis and portal hypertension. Physical examination revealed obesity (BMI 34.9kg/m2) and acanthosis nigricans. Blood exams showed leucopenia and thrombocytopenia without anemia, compatible with portal hypertension. Chest CT revealed important dilatation of the pulmonary arteries, a nodular liver and splenomegaly. Liver biopsy confirmed cirrhosis. An extensive workup including whole exome sequencing identified a homozygous *MC4R* variant [NM_005912.2 (*MC4R)*: c.63_64del, p.(Tyr21*)], classified as pathogenic according to the ACMG guidelines. Both parents were heterozygous for this variant. An endocrinological workup showed insulin resistance with a HOMA-IR index of 7.27 and diabetes with peak blood glucose of 11.5mmol/l. HbA1c was 5.1% (32mmol/mol). Thyroid tests, leptin, proinsulin levels (3.5pmol/l, n <11.0pmol/l) were normal.

The mutation being homozygous with a predicted complete loss of function (https://www.mc4r.org.uk/), no treatment with a MC4R agonist was tried. At the age of 15 years (BMI 36.0kg/m2), the patient underwent liver transplantation because of progressive portal hypertension and to halt the progression of pulmonary hypertension. At the age of 16 years (BMI 33.2kg/m2, HbA1c 4.9% (30.0 mmol/mol), HOMA-IR 5.3) a treatment with GLP-1 RA (liraglutide) was started at a dosage of 0.6mg and progressively increased to 3mg, in an attempt to induce weight loss, avoid the accumulation of liver fat and to protect the graft. GLP-1 RA is supposed to exerts its effects on appetite independently of the MC4R pathway. 2 months after liraglutide introduction, no side effects, a weight loss of 4kg and a decrease of appetite were observed (BMI 31.6kg/m2, HbA1c 4.5% (26mmol/mol), HOMA-IR 3.14).

Conclusion

Obesity-associated *MCR4* mutations, in homozygous state, may lead to diabetes, liver cirrhosis and porto-pulmonary hypertension. Treatment options are scarce, but GLP-1 RA seem to have a rapid, positive effect on weight and metabolic control. Would earlier treatment have prevented progression to end-stage-liver disease and need for liver transplantation?

Diabetes Mellitus and Glucose Metabolism

DIABETES COMPLICATIONS II

Euglycemic Diabetic Ketoacidosis Associated with SGLT-2 Inhibitors- an Under-recognized Diagnosis

Sarah Chhabra, MD[1], Alex Manzano, MD[2], Neha Garg, MD[3].
[1]Mount Sinai Medical Center, Miami, Miami, FL, USA, [2]The Thyroid, Parathyroid and Pituitary Center for Miami, South Miami, FL, USA, [3]MOUNT SINAI MEDICAL CENTER, Miami, FL, USA.

MON-690

Euglycemic Diabetic Ketoacidosis Associated With SGLT- 2 Inhibitors - An Under- recognized Diagnosis

Background

Sodium glucose cotransporter-2 inhibitors (SGLT-2i) are a promising class of oral anti-hyperglycemic agents with mounting evidence of reduced cardiovascular risk and renal failure, in patients with type 2 diabetes mellitus. Recent increase in their use has led to identification of hitherto unknown side effects of these drugs. Euglycemic Diabetic Ketoacidosis (eDKA), found to be associated with SGLT-2i use, is a life-threatening condition and commonly goes unrecognized due to absence of the cardinal sign of hyperglycemia.

Clinical Case