Clinical Case: A 22-year-old male patient was referred to the endocrine clinic in 2018 with recent -onset hyperglycemia. His weight was 82.2 kg with a height of 180 cm (BMI of 25.3 kg/m^2). Physical examination revealed small testes, micropenis, and no axillary and pubic terminal hair. His smell sense was intact. His hormonal test reveals low testosterone (0.10 ng/mL) and low free testosterone (0.65 pg/mL) levels with inappropriately low gonadotrophins levels. Secretion of LH and FSH increased 2-fold after GnRH stimulation. His bone age was 13-years 6-months old, and brain magnetic resonance imaging showed the presence of olfactory bulbs, and unremarkable findings except for small size of the pituitary gland. There were no signs associated with CHARGE syndrome (coloboma ocular, heart defects, atresia or stenosis of the choanae, retardation of growth and/or development, genitourinary anomalies, and ear abnormalities). Biochemical investigation demonstrated high serum glucose level and high HbA1c (13.8%). To identify variants to cause the phenotype of the proband, we adopted trio-based whole exome sequencing (WES) and candidate gene approach. Candidate genes was listed from the orphanet (*https://www.orpha.net*). WES of the proband revealed the presence of heterozygote missense mutations of the *CHD7* gene (c.6107C>T, p.Pro2036Leu, rs369543203) and *PCSK1* gene (c.239G>A, p.Arg80Gln, rs1799904). The missense variants were predicted to have a damaging effect on the encoded protein, by SIFT and PolyPhen-2 analyses. Genetic analyses of his family revealed that his father had the same heterozygote missense mutations of the *CHD7* gene, but wild type of *PCSK1*. Proband's mother had the same heterozygote missense mutations of *PCSK1*, but wild type of *CHD7*. Furthermore, the proband had homozygote missense mutation of *PAX4* (c.575G>A, p.Arg192His, rs2233580) known as maturity-onset diabetes of the young (MODY) 9 gene. Both parents have the same but heterozygous mutation of *PAX4* p.Arg192His, and pre-diabetic range of hyperglycemia.

Conclusion: This is the first case demonstrating digenic inheritance of mutations in *PCSK1* and *CHD7* as a potential cause of normosmic hypogonadotrophic hypogonadism, interestingly in *PAX4* homozygous diabetic male.

Reference: (1) Maione L, et al. Genetic counseling for congenital hypogonadotropic hypogonadism and Kallmann syndrome: new challenges in the era of oligogenism and next-generation sequencing. Eur J Endocrinol. 2018;178(3):R55-R80.

Diabetes Mellitus and Glucose Metabolism

METABOLIC INTERACTIONS IN DIABETES

Hypoglycemic Effect of Oral Administered Superoxide Dismutase

Shutao Liu, Dr, Hangqi Liu, Master.
Fuzhou University, Fuzhou, Fujian, China.

SUN-656

Hypoglycemic Effect of Oral Administered Superoxide Dismutase on Type 2 Diabetes via reduction of glucogan and insulin resistance

Background & Objective: Superoxide dismutase (SOD) is carefully used in food industry for the concern of its easy degradation and difficult adsorption in digestive tract, although it plays central role in antioxidant system. It is previous reported that orally administered SOD was effective in alleviating hyperglycemia, cerebral ischemia-reperfusion and chronic hepatitis. This work aimed to investigate in-depth the hypoglycaemic effect and possible mechanism of orally administered SOD in the model of type 2 diabetic rats.

Methods: The model of type 2 diabetic rats were divided into 6 groups and orally administered with different Cu/Zn-SOD (abbreviated as SOD) samples and negative or positive controls. The 6 groups included SOD, SOD hydrolysate (pepsin-treated SOD), L-SOD (liposome-embedded SOD), model group and metformin positive groups, as well as normal group. Results of the body weight, serum indexes (including blood glucose, glycated albumin, insulin, glucagon, AMPK, MDA), SOD enzymatic activity in organs (liver, heart, kidney, skeletal muscle, spleen, and pancreas) as well as intestinal density and HE staining were measured to evaluate the hypoglycemic effect and possible mechanism.

Results: SOD showed substantial hypoglycemic effect and improved serum indicators. Moreover, L-SOD group exhibited better effect than SOD group, though the effect of SOD hydrolysate was not obvious. Colon density and HE staining showed obvious intestinal injury in the model group, and SOD was beneficial to repair intestinal structural integrity. Furthermore, the reparative effect of SOD was much better than that of the SOD hydrolysate, but not as good as that of the L-SOD. The SOD enzymatic activity of tissues was positively correlated with the curative effect of three kinds of SOD samples. The contents of serum MDA were negatively correlated with the curative effect. Compared with the model group, the insulin resistance index of SOD group, L-SOD group and positive group were significantly reduced; and glucagon significantly decreased by 68.38, 77.50 and 65.01%, respectively.

Conclusion: Oral SOD showed obvious hypoglycemic effect on type 2 diabetic rats, and liposome could improve this effect. The mechanism may be that SOD effectively reduces intestinal injury, so as to reduce glucongen and insulin resistance index.

Steroid Hormones and Receptors

STEROID AND NUCLEAR RECEPTORS

Phosphorylation Site S122 in Estrogen Receptor α Has a Tissue-Dependent Role in Female Mice

Karin L. Gustafsson, PhD student[1], Helen H. Farman, PhD[1], Petra Henning, PhD[1], Vikte Lionikaite, PhD[1], Sofia Movérare-Skrtic, PhD[1], Klara Sjogren, PHD[1], Annica Andersson, PhD[1], Ulrika Islander, PhD[1], Angelina I. Bernardi, PhD[1], Pierre Chambon, MS,MD,BSC[2], Claes Ohlsson, MD,PHD[3], Marie K. Lagerquist, PhD[1].
[1]UNIVERSITY OF GOTEBORG, Gothenburg, Sweden, [2]Institut de Genetique et de Biologie Moleculaire et Cellulaire, Illkirch, France, [3]Sahlgrenska Univ Hosp, Gothenburg, Sweden.

SUN-744

Estrogen treatment increases bone mass and reduces fat mass but is associated with adverse effects in postmenopausal women. Knowledge regarding tissue-specific estrogen

signaling is important to aid the development of new tissue-specific treatments. We hypothesized that the posttranslational modification phosphorylation in estrogen receptor alpha (ERα) may modulate ERα transcriptional activity in a tissue-dependent manner. Phosphorylation of site S122 in ERα has been shown *in vitro* to affect ERα activity, but the tissue-specific role *in vivo* is unknown. We herein developed and phenotyped a novel mouse model with a point mutation at the phosphorylation site 122 in ERα (S122A). Female S122A mice had increased fat mass and serum insulin levels but unchanged serum sex steroid levels, uterus weight, bone mass, thymus weight, and lymphocyte maturation compared to WT mice. In conclusion, phosphorylation of ERα S122 has a tissue-dependent role with an impact specifically on fat mass in female mice. This study is the first to demonstrate *in vivo* that phosphorylation of a transactivation domain in a nuclear steroid receptor modulates its activity in a tissue-dependent manner.

Reproductive Endocrinology

TRANSGENDER MEDICINE AND RESEARCH

Estradiol Dose and Concentrations in Transfeminine Individuals

Brendan J. Nolan, MBBS, FRACP[1], Adam Brownhill, MBBS, MRCGP (UK), FRACGP, FARGP[2], Ingrid Bretherton, MBBS, FRACP[1], Peggy Wong, MBBS, FRACGP[2], Susan Fox, MBBS, FRACGP[2], Peter Locke,[2], Nicholas D. Russell, MBBS, FRACP[1], Mathis Grossmann, MD, PhD, FRACP[1], Jeffrey D. Zajac, MBBS, FRACP, PhD[1], Ada S. Cheung, MBBS, FRACP, PhD[1].
[1]University of Melbourne (Austin Health), Melbourne, Australia, [2]Equinox Gender Diverse Clinic, Melbourne, Australia.

SUN-039

Background: Feminizing hormone therapy with estradiol is used to align an individual's physical characteristics with their gender identity. Australian expert consensus guidelines (1) recommend targeting estradiol concentrations of 250-600 pmol/L (68-163 pg/mL) based on local cross-sectional data (2). We aimed to establish the proportion of individuals achieving estradiol concentrations in consensus guidelines.

Methods: A retrospective cross-sectional analysis was performed of transfeminine individuals attending a primary or secondary care clinic in Melbourne, Australia who were prescribed oral estradiol valerate for at least 6 months and had estradiol dose and concentration available. Estradiol concentration was measured by immunoassay. Outcomes were (1) proportion of individuals achieving target estradiol concentrations and (2) influence of estradiol dose and BMI on estradiol concentrations.

Results: 259 individuals (median age 25.8(IQR 21.9,33.5) years)) had data available for analysis. Median duration of estradiol therapy was 24(15,33) months. Median estradiol concentration was 328(238,434) pmol/L (89(65,118) pg/mL) on 6(4,8) mg estradiol valerate. 172 (66%) individuals had estradiol concentrations within the target range recommended in consensus guidelines. 70 (27%) individuals had estradiol concentrations below target, and 17 (7%) above target. There was a weak positive correlation between estradiol dose and estradiol concentration (r=0.156, p=0.012). There was no correlation between BMI and estradiol concentration achieved (r=-0.063, p=0.413).

Conclusions: 66% of individuals achieved estradiol concentration recommended in consensus guidelines with a relatively high oral estradiol dose. There was significant interindividual variability. Estradiol concentration should be interpreted in conjunction with clinical features of feminization and weighed against potential risks of escalating estradiol dose.

References

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Thyroid

THYROID DISORDERS CASE REPORTS III

A Case of Inoperable Substernal Goiter

Garyfallia Papaioannou, MD, PhD[1], Erick Perez Sifontes, MD[1], Gnanambal Manivel, MD[1], Manivel Kumaran Eswaran, MD, MS[2].
[1]University of Central Florida College of Medicine, North Florida Regional Medical Center Internal Medicine Residency Program, Gainesville, FL, USA, [2]University of Central Florida College of Medicine, North Florida Regional Medical Center Internal Medicine Residency Program, Accent Physician Specialists, Endocrinology, Gainesville, FL, USA.

MON-467

Introduction: Goiter is abnormal growth of the thyroid gland. When goiter extends into the mediastinum it is called retrosternal or substernal. Substernal goiter can cause compression of the great vessels, trachea, and esophagus. When it compresses trachea it can result in airway obstruction. In that case treatment of choice is thyroidectomy and Radio Iodine Ablation (RIA). But some patients are considered to be high risk for operation due to multiple comorbidities. We are presenting this case where we tried experimental therapy with airway stent and external beam radiation. **Case:** An 81 year old female presented to the hospital complaining of chest pain. She also reported dysphagia to solids and liquids and weight loss during one month. Past medical history included congestive heart failure, atrial fibrillation, chronic obstructive pulmonary disease with home oxygen support. On physical exam thyroid was palpable to the level of sternal notch. Arterial blood gases showed hypoxemia (PO2 63), thyroid function tests showed an abnormally suppressed TSH (<0.005 IU/ml), elevated free T4 (2.48 ng/dl) and normal T3. Thyroid stimulating immunoglobulin, IgG, IgM and IgA levels were normal. Thyroglobulin and thyroid peroxidase antibodies were negative. Chest X-ray revealed an upper mediastinal mass. Chest CTA showed a very large substernal goiter with left thyroid lobe of 7.4 x 3.4 x 7.8 cm that extended to the level of the carina causing compression of the