Medical Center/Wayne State University Endocrine Fellowship Program, Detroit, MI, USA, [3]Wayne State University, Dearborn Heights, MI, USA.

MON-LB116

Background and aims: Fibroblast growth factor (FGF)-21 is a polypeptide that results in metabolic rearrangement mostly related to glucose and lipid metabolism. Serum FGF-21 level is elevated in obesity and in type 2 diabetes. The goal of this study is to evaluate the relationship between FGF-21 and peripheral insulin resistance in a wide range of baseline BMI and glucose metabolism status. Materials and methods: seventy one participants reported to the clinical research center in a fasting state twice. BMI and fat mass were calculated. Glucose metabolism was determined by fasting glucose, hemoglobin A1c and OGTT. Serum lipids panel was measured. Peripheral insulin resistance was determined using the hyperinsulinemic euglycemic clamp study. FGF-21 level was measured using enzyme-linked immunosorbent assay before and after clamp study. Study was approved by university institutional review board. Results: Of 71 participants, 48 were obese and 23 were lean. Normal glucose metabolism was documented in 43 individuals. Serum FGF-21 was significantly elevated in insulin resistant compared to insulin sensitive subgroups (0.28 ng/ml ± 0.136 vs. 0.14 ng/ml ± 0.112. $p < 0.001$). Despite the fact that FGF-21 is elevated in all obese population, the level was significantly higher in the insulin resistant obese subgroup compared to the insulin sensitive obese one (0.30 ng/ml ± 0.167 vs. 0.17 ng/ml ± 0.126. P =0.003). Furthermore, significantly higher FGF-21 level was also found in lean insulin resistant compared to lean insulin sensitive subgroups (0.18 ng/ml ± 0.106 vs. 0.09 ng/ml ± 0.061, p = 0.04]. Adjustment to pre-existing impaired glucose tolerance did not affect the correlation between FGF-21 level and insulin resistance which remained statically significant in the seemingly healthy obese and lean subgroups. Conclusion: Serum FGF-21 level strongly correlates to peripheral insulin resistance in both obese and lean population. Nonetheless, FGF-21 level rises way before glucose metabolism abnormality can be detected. Our study suggests a cutoff level for each subgroup which may enable clinicians to risk-stratify patients and allow for early intervention.

Neuroendocrinology and Pituitary

PITUITARY TUMORS II

Impact of Imputation Method and Response Cutoffs on Results From the Phase 3 OPTIMAL Study of Oral Octreotide Capsules in Adult Patients With Acromegaly

Susan Leanne Samson, MD, PhD[1], Lisa B. Nachtigall, MD[2], Maria Fleseriu, MD[3], Murray B. Gordon, MD[4], Mojca Jensterle, MD, PhD[5], Atanaska Elenkova, MD, PhD[6], William Henry Ludlam, PhD, MD[7], Gary Patou, MD[8], Asi Haviv, DMD[8], Nienke Biermasz, MD, PhD[9], Peter James Trainer, BSc, MBChB, FRCP, MD[10], Christian Joseph Strasburger, MD[11], Laurence Kennedy, MBBS, MD, FRCP[12], Shlomo Melmed, MD[13].

[1]Baylor College of Medicine, Houston, TX, USA, [2]MGH Neuroendocrine and Pituitary Center, Chestnut Hill, MA, USA, [3]Oregon Health & Science University, Portland, OR, USA, [4]Allegheny General Hospital, Pittsburgh, PA, USA, [5]University Medical Centre Ljubljana, Ljubljana, Slovenia, [6]Department of endocrinology, Medical University Sofia, USHATE "Acad. Ivan Penchev", SOFIA, Bulgaria, [7]Chiasma, Mountain Lakes, NJ, USA, [8]Chiasma, Waltham, MA, USA, [9]Leiden University Medical Center, Oegstgeest, Netherlands, [10]The Christie NHS Foundation Trust, Manchester, United Kingdom, [11]Charite Campus Mitte, Berlin, Germany, [12]Cleveland Clinic Foundation, Cleveland, OH, USA, [13]Cedars Sinai Medical Center, Los Angeles, CA, USA.

MON-LB57

Objective: The phase 3 CHIASMA OPTIMAL study assessed efficacy and safety of oral octreotide capsules (OOC) in patients with acromegaly controlled on injectable somatostatin receptor ligands (SRLs). Sensitivity analyses were conducted for efficacy endpoints using two methods of imputation (i.e., the process of replacing clinical data with substitution values) to address missing data points due to some subjects reverting back to their prior injectable SRL treatment. **Methods:** Patients were ≥18 years of age and had evidence of active acromegaly with an average IGF-I ≤ 1.0 x ULN (utilizing the IDS iSYS assay calibrated to WHO recombinant reference standard 02/254). At baseline, patients were randomized to receive OOC or placebo for 36 weeks. The primary endpoint was proportion of patients maintaining biochemical response, defined as IGF-I ≤1.0 x ULN (2-value average at weeks 34 and 36) (Samson et al. ENDO 2020). Per study protocol, patient study discontinuations were considered non-responders regardless of clinical response at the time of discontinuation (non-response imputation). Additional exploratory analyses were performed utilizing the last observation carried forward (LOCF) analysis, as well as a completers analysis of response among the subgroup that completed the entire 36 weeks on study drug. The response rates reported for the primary end point are slightly adjusted for stratification differences as prespecified in the statistical analysis plan. **Results**: Twenty-eight patients received OOC and 12 failed to maintain biochemical response based on the primary endpoint. Seven of these 12 patients discontinued treatment early - 5 due to treatment failure and 2 due to AEs. The remaining 5 patients completed the 36-week protocol on study drug. Of these 5 patients, 4 had IGF-I values between >1.0 and ≤1.3 x ULN and 1 completed the study with an IGF-I of 1.7 x ULN with no clinical symptoms. 58.2% of patients in the OOC group met the primary endpoint of maintenance of biochemical response at the end of study using the non-response imputation. Using LOCF imputation, 64.3% (18/28) of patients met this endpoint. Of those completing the study (N=21), 76.2% maintained response. **Conclusion:** CHIASMA OPTIMAL primary endpoint was assessed using the non-response imputation for patients who discontinued treatment early, with a 58.2% response rate. However, when assessing the response rate based on LOCF imputation, or in study completers, similar to other phase 3 studies for acromegaly, the rate was imputed at 64.3% and 76.2%, respectively.