Objective: To evaluate the diagnostic performance of a sensitive immunoassay for p-insulin and to find the optimal p-insulin cut-off for CHI versus other conditions with hypoglycaemia.
Design: Single centre retrospective cohort study.
Methods: Diagnostic tests with no medication, no i.v. glucose and under fasting conditions were performed in children with a clinical diagnosis of CHI. P-insulin concentrations determined at simultaneous p-glucose concentrations at least <3.2 mmol/L (57.5 mg/dL) were included in the analysis (n=61).
The diagnosis of CHI was either clinical (n=61) or by gold standard criteria: hypoketotic hypoglycaemia plus disease-causing genetic mutations and/or diffuse, focal or atypical pancreatic histopathology (n=57). Samples from 15 children with idiopathic ketotic hypoglycaemia (IKH, diagnosis by exclusion, p-ketones >1.5 mmol/L during hypoglycaemia) were used as controls.
P-insulin was measured by the high-sensitive assay (Cobas e411 immunoassay analyzer); lower detection limit 1.4 pmol/L (0.2 mU/L); normal range 18-173 pmol/L (2.57-24.7 mU/L). Concentrations <18 pmol/L were considered suppressed; ≥18 pmol/L un-suppressed.
Receiver operating characteristics (ROC) curves with determination of area under the curve (AUC) values were performed for the diagnostic performance of p-insulin in the diagnosis of CHI. *Results:* In the 61 samples from CHI patients, the median (range) p-insulin was un-suppressed in all diagnostic samples [90; 20-758 pmol/L (12.9; 2.9-109.1 mU/L)], while p-insulin was suppressed in all 15 samples from IKH patients [1.5; 1.5-9 pmol/L (0.21; 0.21-1.3 mU/L)]. The ROC AUC was 1.0 (95%CI. 1.0-1.0) for the diagnosis of CHI defined both by the clinic and by gold standard. The optimal p-insulin cut-off was 14.5 pmol/L (2.1 mU/L) or 12.5 pmol/L (1.8 mU/L), for CHI patients by use of a simultaneous p-glucose cut-off of <3.2 mmol/L (57.5 mg/dL; n=61), or 3.0 mmol/L (55 mg/dL; n=49), respectively.
Conclusions: The sensitive insulin assay performed excellent in diagnosing CHI with a ROC AUC of 1.0. The use of a p-insulin cut-off of 13 pmol/L (1.86 mU/L) during a diagnostic hypoketotic hypoglycaemia test may establish the diagnosis of CHI without further diagnostic testing.

Diabetes Mellitus and Glucose Metabolism

DIABETES TECHNOLOGY

Results of a Preclinical Pilot Study Evaluating 24-Hour Subcutaneous Infusion of the GLP-1 Analogue Liraglutide Delivered via the H-Patch Wearable Device

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SAT-635

Nonalcoholic fatty liver disease (NAFLD) affects an estimated 30% of Americans, is the most common cause of chronic liver disease in the US, and a leading cause of liver-related morbidity/mortality worldwide[1]. Currently, there are no FDA-approved drugs specifically tailored to NAFLD or its big brother, non-alcoholic steatohepatitis (NASH). Glucagon-like peptide 1 (GLP-1) is an incretin peptide hormone, secreted in the distal ileum and proximal colon by L cells. Besides stimulating the pancreas to cause beta cell proliferation and enhance insulin biosynthesis, GLP-1 interacts with receptors in other parts of the GI tract, lung, kidney and CNS. Thus, GLP-1's metabolic functions include delayed gastric emptying, appetite suppression, enhanced liver glucose uptake, peripheral insulin sensitivity, as well as glucose-dependent insulin secretion while inhibiting the release of glucagon from α-cells. While GLP-1 receptor agonists such as exenatide and liraglutide have been approved for type 2 diabetes, a meta-analysis of several studies has shown promise in patients with NASH. Effects including decreased serum ALT levels, improvement in hepatic fat content and fibrosis, and weight loss making GLP-1 therapeutics potentially attractive for use in patients with NASH and metabolic syndrome[2-5]. While subcutaneous injection is an avenue for administration, continuous infusion offers many benefits for native GLP-1 and GLP-1 analogues. We investigated the pharmacokinetics (PK) of a GLP-1 analogue (liraglutide) delivered over a single 24h period using the wearable h-Patch™ subcutaneous infusion device in dogs. Liraglutide (1800ug) was infused at a static rate over 24h delivered with PK evaluated at time points to 72h from the start of infusion. Liraglutide levels were detectable in blood detected within 30m of the beginning of infusion, peaked above the upper level of quantitation of the LC/MS/MS analysis (316ng/ml upper level of quantitation), and gradually decreased with quantifiable levels still detected 48h after completion of h-Patch™ infusion. The h-Patch™ provides a simple all-in-one delivery device with no exposed needle, no programming or infusion set required, additionally it can be configured to deliver two payload in separate reservoirs offering the potential option of an insulin/GLP-1 infusion combination. These preliminary encouraging results of liraglutide infusion via the h-Patch warrant further investigation in a variety of indications including diabetes, NASH, and obesity as a monotherapy and in combination with other complementary therapeutics. 1. Liver Int. 2017; 37(S1):97-103. 2. Lancet. 2016; 387(10019):679-690. 3. J Gastroenterol Hepatol. 2016; 31(1):23-31. 4. Clin Ther. 2007; 29(1):139-153. 5. Aliment Pharmacol Ther. 2013; 37(2):234-242.

Diabetes Mellitus and Glucose Metabolism

CLINICAL STUDIES IN OBESITY, DIABETES RISK, AND CARDIOVASCULAR OUTCOMES

Predictive Ability of Lipoprotein Insulin Resistance (LPIR) Score in South Asians: A Comparison of Surrogate Indices of Insulin Sensitivity/Resistance

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SAT-624

South Asians (SA) are at higher risk for developing insulin resistance (IR) and type 2 diabetes. Consequently, identifying IR in this population is important. Lack of

standardization and harmonization of insulin assays limit the clinical use of insulin-based surrogate indexes of insulin resistance. The lipoprotein insulin resistance (LPIR) score, a metabolomic marker, reflects the lipoprotein abnormalities observed in insulin-resistant states. The reliability of the LPIR score to predict IR in South Asians is currently unknown. In this study, we aimed to evaluate the predictive accuracy of LPIR compared to other fasting-based surrogate indices in SA.

In a cross-sectional study of 59 non-diabetic SA subjects (age 36 ± 8 years, BMI 26.5 ± 5.2 kg/m^2), we used calibration model analysis to assess the ability of the LPIR score and other simple surrogate indices [homeostasis model assessment (HOMA-IR), quantitative insulin sensitivity check index (QUICKI) and Adipose tissue insulin sensitivity (Adipo-SI)] to predict insulin sensitivity derived from the reference frequently sampled intravenous glucose tolerance test (FSIVGTT) and Minimal Model analysis (SiMM). LPIR scores were calculated using six lipoprotein particle concentrations and sizes measured by nuclear magnetic resonance (NMR) spectroscopy. Further, quantitative predictive accuracy and index comparisons were determined by root mean squared error (RMSE) of prediction and leave-one-out cross-validation-type RMSE of prediction (CVPE). Receiver operating characteristic (ROC) curve analysis was performed to determine how well LPIR distinguished insulin resistant individuals, categorized as an SiMM < 3.

As determined by calibration model analysis, Adipo-SI, HOMA-IR, and QUICKI showed moderate correlations with for SiMM (Adipo-SI: r = 0.66; HOMA-IR: r = 0.60; QUICKI: r = 0.57, p = <0.0001). No significant differences were noted among CVPE or RMSE from any of the routinely used surrogate indices when compared with LPIR. The ROC area under the curve was 0.76 (95% CI 0.64–0.87) suggesting that LPIR performed well in identifying insulin resistant subjects. The optimal cut-off in IR individuals was LPIR >46 (sensitivity: 75.9 %, specificity: 70.0%). We conclude that NMR-derived LPIR may be an appropriate index to assess insulin resistance in South Asians.

Cardiovascular Endocrinology

ENDOCRINE HYPERTENSION AND ALDOSTERONE EXCESS

Can Histology Predict the Presence of KCNJ5 Somatic Mutation in Aldosterone-Producing Adenomas?

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SAT-555

Aldosterone-producing adenoma (APA) is well known to harbor marked intratumoral heterogeneity in terms of morphology and CYP11B2 (aldosterone synthase) localization. In histology, APA is generally characterized by two distinct cell subtypes, namely “clear cells” and “compact cells”. Clear tumor cells harbor abundant lipid droplets in their cytoplasms and compact tumor cells generally featuring small round shape have abundant intracytoplasmic organelles including mitochondria.

Relatively close correlation between these histological characteristics (morphology and CYP11B2 immunohistochemistry) and genotypes of aldosterone-driver gene somatic mutation has been reported. Among them, *KCNJ5*-mutated APAs have been reported to harbor clear cell predominant features, while APAs with other rare somatic mutations including *ATP1A1*, *ATP2B3* and *CACNA1D* harbor heterogenous or relatively compact cell predominant morphometry. However, these previous evaluation were based on eyeball analysis with relatively low reproducibility. Therefore, we developed the more quantitative methods using digital image software in order to analyze the widespread area, which can reflect intratumoral heterogeneity, with high reproducibility to analyze the further detailed correlation between histopathological characteristics and genotype in APA. We explored the utility of immunohistochemistry including CYP11B2 and KCNJ5. We further attempted to propose histopathological scoring system to predict the presence of *KCNJ5* somatic mutation in APAs.

Results of our present study revealed that KCNJ5 was predominantly immunolocalized in zona glomerulosa among adrenal cortex (vs. ZF, P=0.0002, vs. ZR, P=0.0002), furthermore, predominantly in APCCs than in non-APCCs (P=0.0019). Among the tumors, KCNJ5 immunoreactivity was significantly higher in *KCNJ5*-wild type APAs than in mutated ones (P=0.0037). *KCNJ5*-mutated APAs had significantly lower nuclear / cytoplasm ratio and abundant clear cell components than those with wild type, harboring large tumor size. In conclusion, we firstly proposed a novel histopathological predicting scoring system for the presence of *KCNJ5* somatic mutation, including the following histopathological findings; N/C ratio, clear cell (%), tumor size, CYP11B2 immunoreactivity and KCNJ5 immunoreactivity. It is true that no single histological factors above could precisely predict the presence of *KCNJ5* somatic mutation but this newly developed combined histopathological predicting scoring system could provide relatively high accuracy to predict *KCNJ5* somatic mutation in APAs (AUC=96%, sensitivity:100%, specificity:90%, 4 points or more). However, further prospective validation by large number of cases is required for clarification.

Adrenal

ADRENAL CASE REPORTS I

Primary Adrenal Lymphoma Presenting with Symptomatic Hypercalcaemia

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