21st Annual World Congress on Insulin Resistance Diabetes and Cardiovascular Disease (WCIRDC)

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Abstract Oral Presentation Session
Friday December 8, 2023
7:30pm – 9:00pm
Sierra Ballroom C/D

(Cheese and Wine will be served)

All Abstracts are published in 'Metabolism' Journal
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Awards will be presented on Saturday December 9th
At the main session hall at: 8:00am

All 21st WCIRDC posters can be viewed on the virtual platform.
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21st WCIRDC
Oral Presentations

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0035
Reduced Lipotoxicity Following Triple Therapy for 3 Years in New Onset T2DM

Authors
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Abstract
We previously have shown that transition from NGT to IGT to T2DM is associated with a progressive increase in plasma FFA concentration and adipocyte insulin resistance (adipo-IR) (Diabetes 66:815-822, 2016). In the EDICT study, we demonstrated that initial Triple Combination therapy with drugs (pioglitazone, exenatide, metformin) that correct the basic pathophysiologic defects in T2DM was markedly superior than stepwise Conventional therapy (metformin → add SU → add glargine insulin) in reducing A1c and improving insulin resistance and beta cell function in newly diagnosed T2DM after 3 years (Diabetes Care 44:433-439, 2021). Herein, we compared the effect of Triple Combination therapy (n=79) versus Conventional (n=69) therapy on plasma FFA and adipo-IR and their relationship to insulin resistance, beta cell function, and hepatic steatosis/fibrosis (Fibroscan). Fasting adipo-IR (FPI x F-FFA) decreased by 50% (10.1±0.9 to 5.1±0.5, $p<0.001$) in Triple Therapy after 3 years and increased by 14% in Conventional Therapy ($p<0.001$). Adipocyte insulin sensitivity during OGTT ($\Delta FFA/\Delta I$) increased 3-fold in Triple Therapy (0.010±0.003 vs 0.03±0.001, $p<0.001$) and was unchanged in Conventional Therapy (0.12±0.001 vs 0.012±0.003) ($p<0.001$ vs Triple Therapy). During OGTT (0-120 min), ΔC-peptide (6.5±0.6 to 9.5±0.9, $p<0.001$) and Matsuda insulin sensitivity index (3.3±0.5 to 9.8±0.2, $p<0.001$) increased markedly in Triple Therapy, with no change in Conventional Therapy. Only insulin secretion in subjects receiving Triple Therapy measured with ΔCPEP0-120 at the end of study strongly correlated with FFA suppression ($r=0.52$, $p<0.01$). Neither fasting FFA nor FFA during OGTT correlated with CAP (hepatic steatosis) or kPa (hepatic fibrosis). CONCLUSION: reduced lipotoxicity contributes to enhanced beta cell function and insulin sensitivity following Triple Therapy.

Keywords: Lipotoxicity, Insulin resistance, hepatic steatosis, fibrosis

Abbreviation: T2DM type 2 diabetes mellitus, FFA free fatty acid, OGTT oral glucose tolerance test, NGT normal glucose tolerance, IGTimpaired glucose tolerance

Funding Disclosure: This study was supported by the National Institutes of Health grant R01DK24092-34 to R.A.D.

Conflict of Interest: Olga Lavrynenko, MD, PhD, Muhammad Abdul-Ghani, MD, PhD declare that they have no conflict of interest.
RALPH A. DEFRONZO, MD (DISCLOSURES – 2023)
Advisory Board: AstraZeneca, Novo Nordisk, Boehringer-Ingelheim, Intarcia, Renalytix, Corcept Therapeutics
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Ethical approval: Participants provided written informed consent, and research protocols and procedures were approved according to the ethical standards of the Helsinki Declaration 2013

0044

Carbohydrate Restriction-Induced Elevations in LDL-Cholesterol and Atherosclerosis: The KETO Trial

Authors

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Abstract

Introduction: While most individuals who adopt carbohydrate restricted ketogenic diets for obesity or diabetes exhibit improvements in lipid parameters, some who adopt these diets exhibit increases in LDL-cholesterol (LDL-C). A population of these individuals, termed lean-mass hyper-responders (LMHRs) – previously defined by the metabolic triad of elevations in LDL-C and HDL-C with low triglycerides on a carbohydrate-restricted diet – exhibit extreme increases in LDL-C. It is unknown, in this context of otherwise good metabolic health, whether or to what degree the increases in LDL-C induced by carbohydrate restriction may accelerate atherosclerosis. The aim of this study is to prospectively evaluate the plaque progression over the course of 1-year in 100 metabolically health LMHR subjects on a ketogenic diet with LDL-C ≥190 mg/dl. Herein, we present the baseline characteristics of the cohort and pre-specified analysis of quantitative plaque measures from coronary CT angiography (CCTA) data in the 100 LMHR subjects, with matching to subjects from The Miami Heart Study (MiHeart), a population based study of atherosclerosis with participants undergoing CCTA.

Methods: 80 LMHR or near-LMHR asymptomatic subjects with LDL-C ≥ 190, HDL-C ≥ 60, and triglycerides ≤ 80 mg/dl were matched 1:1 for age, gender, race, diabetes mellitus, hyperlipidemia, hypertension, and past smoking to asymptomatic subjects from the MiHeart cohort. The 20 LMHR subjects not matched were outside the MiHeart cohort age range of 40-65 years. LMHR followed a ketogenic diet (very low carb diet), usually <30g/d, sufficient to induce an elevation in circulating ketone bodies, which was measured and was required to be elevated in these participants to be enrolled. Primary analysis were levels of Coronary Artery Calcium (CAC), Total Plaque Score (TPS), Total Stenosis Score (TSS) and Segment Involvement Score (SIS), analyzed with the Wilcoxon Rank Sum test. All measures were done in the same CT laboratory by expert readers blinded to all clinical variables and diet information.

Results: The mean age of the LMHR cohort was 55.3 ± 10.3, 59% male, with mean LDL-C of 272 ± 91 mg/dl [max LDL-C 591 mg/dl], matched 1:1 to Miami Heart cohort, with similar age, sex, race/ethnicity and risk factors including systolic, diastolic blood pressures, smoking history, diabetes, hemoglobin A1c (all p>0.05) and LDL-C of 123±38 mg/dl. Mean duration of ketogenesis was 4.7±2.8 years at time of CCTA. There was no significant difference in the LMHR subjects total CAC score (median and IQR)[0 (0,56)] versus in MiHeart[1(0, 49)],p = 0.520 and no significant difference in the CCTA outcomes; TSS[0 (0,3) versus 1(0,3),p=0.357], TPS[0(0,2) versus 1(0,4),p=0.357], and SI[0 (0,2) versus 1(0,3),p=0.366]. Further, there was no significant correlation between LDL-C level and CCTA plaque metrics (Figure 1).

Conclusion: After a mean duration of 4.7 years of carbohydrate restriction-induced elevations in LDL-cholesterol, a metabolically healthy cohort of subjects on a ketogenic diet did not have greater atherosclerotic burden than participants from a population based cohort with similar risk profiles but markedly lower LDL-C.

Keywords: Ketogenic Diet; coronary atherosclerosis, CT angiography, Miami Heart Study

Abbreviations (Up To Five): lean-mass hyper-responders (LMHRs); LDL Cholesterol - low density lipoprotein; CCTA - coronary computed tomographic angiography; high density lipoprotein (HDL), coronary artery calcium (CAC)

Funding Disclosure: Funding for this study was obtained from the Citizens Science Foundation

Conflict Of Interest: Dr Budoff receives grant support from General Electric

Ethical Approval Disclosure: This study was approved by the IRB of Lundquist Institute.

0071

FIGARO-BM, a Biomarker Study of FIGARO-DKD, Reveals New Insights Into the Mode-of-Action of Finerenone

Authors

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Abstract

Background: Mineralocorticoid receptor (MR) overactivation contributes to tissue fibrosis and end-organ damage found in cardiorenal disease.
Objective: The exploratory biomarker study, FIGARO-BM, aims to advance the understanding of the longitudinal pharmacodynamic response to finerenone, a non-steroidal, selective MR antagonist.

Methods: Samples were derived from the phase III parent trial FIGARO-DKD, which investigated finerenone's efficacy on cardiorenal outcomes and safety in patients with CKD and T2D. This substudy included 945 subjects from 21 countries, overall comparable to the total population; 2941 biomarkers in >4000 longitudinal post-randomization plasma samples were analyzed using Olink EXPLORE proteomics. Eligible subjects were on treatment with either placebo or finerenone for ≥24 months. Biomarkers with a significant difference ($p \leq 0.05$) between treatment arms at ≥1 study visit and with effect estimates above threshold were used for gene set enrichment analysis. Enriched terms were grouped into clusters based on membership similarities.

Results: 373 plasma protein biomarkers were modulated by finerenone treatment. Two clusters of extracellular matrix (ECM)-related pathways were identified, involving inflammation and fibrosis markers, e.g. fibronectin, osteopontin, and interleukin-17 family members, along with novel ECM remodeling markers. Other clusters linked directly to mineralocorticoid/aldosterone biology reflecting target modulation.

Conclusion: For the first time, FIGARO-BM provides human biomarker evidence that finerenone acts on inflammation and fibrosis pathways, one key driver of cardiorenal disease progression in T2D. The study supports preclinical findings from animal models and provides insights to mechanisms leading to clinical benefits in a broad cardiorenal patient population. Future studies are needed to validate these findings.

Keywords: Biomarker, Finerenone, Inflammation, Fibrosis, Mineralocorticoid receptor

Abbreviations (Up To Five): Extracellular matrix (ECM), mineralocorticoid receptor (MR)

Funding Disclosure: The study and this analysis were funded by Bayer AG, Wuppertal, Germany.

Conflict Of Interest: This study was first presented on November 2nd 2023 at the American Society of Nephrology's (ASN) Kidney Week in Philadelphia, U.S.A.
MB is an employee of Bayer AG, Germany.
LC is an employee of Bayer UK, Great Britain.

LG is an employee of Bayer AG, Germany.
PK is an employee of Bayer AG, Germany.
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SV is an employee of CHRESTOS Concept GmbH & Co. KG, Germany, a contract partner of Bayer.
KR is an employee of Bayer AG, Germany.
JHI has served on advisory boards for Bayer, AstraZeneca, Akebia, and AlphaYoung, has served as a member of a DSMB for Sanifit International, and has received grants support from Bayer International and the Juvenile Diabetes Research Foundation
FZ has received personal fees from Boehringer Ingelheim during the conduct of the study; has received personal fees from Janssen, Novartis, Boston Scientific, Amgen, CVRx, AstraZeneca, Vifor Fresenius, Cardior, Cereno Pharmaceutical, Applied Therapeutics, Merck, Bayer, and Cellprothera; and is cofounder of CVCT and Cardiorenal, outside the submitted work.
PR has received grants from AstraZeneca, Bayer, Novo Nordisk A/S, as well as consulting fees from AstraZeneca, Astellas, Bayer, Boehringer Ingelheim, Gilead, Merck, Mundipharma, Novo Nordisk A/S and Sanofi. All fees to Steno Diabetes Center Copenhagen
HJLH is a consultant for AstraZeneca, Bayer, Boehringer Ingelheim, Chinook, CSL Behring, Dimerix, Eli Lilly, Gilead, Janssen, Merck, Mitsubishi Tanabe, Novartis, Novo Nordisk and Travere. He received research support from AstraZeneca, Boehringer Ingelheim, Janssen and Novo Nordisk.
TK is a Bayer employee.

Ethical Approval Disclosure: FIGARO-BM was approved by ethical committees and regulatory authorities and complied with the Declaration of Helsinki. All patients provided written informed consent to the biomarker study.

0077

Single-dose GLP-1-based Pancreatic Gene Therapy Maintains Weight Loss After Semaglutide Withdrawal in a Murine Model of Obesity

Authors

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Abstract

Background: GLP-1-based therapies demonstrate clinical efficacy in obesity, yet durability of effect remains a challenge with most patients regaining weight post-treatment discontinuation. We've developed a novel AAV gene therapy platform enabling durable production of therapeutic proteins by the pancreas. Here, we assessed the efficacy and durability of a single-dose, GLP-1-based, pancreatic gene therapy (PGTx) compared to daily semaglutide (Sema) in a murine, diet-induced, obesity model.

Methods: C57BL/6 mice were fed a 60% high-fat diet for 25 weeks and then randomized by body weight (BW) into groups: single-dose i.p. PGTx (1e13 VG, n=10), daily s.c. Sema (10 nmol/kg/d x 4 weeks, n=10), i.p. PGTx vehicle control (n=8), and daily s.c. Sema vehicle control (n=8). Sema was subsequently withdrawn on day 29, and mice were given PGTx (5e12 VG, n=5) or vehicle (n=5). Mean BW and food intake were measured daily over 57 days.

Results: Treatments were well-tolerated. On day 28 post-treatment, BW was reduced by 27% with single-dose PGTx vs. 21% with daily Sema ($p<0.05$). PGTx-induced BW loss was maintained to 57 days post-treatment ($p<0.0001$). Sema withdrawal resulted in regain of BW to -2% below baseline, while treatment of Sema-withdrawn animals with PGTx stabilized 28-day BW loss at -22% below baseline at day 57 ($p<0.01$). Mean food intake paralleled BW changes in all treatment groups.

Conclusions: Single-dose PGTx can durably reduce BW and can also maintain BW reduction upon Sema withdrawal. These data suggest that PGTx has the potential to advance GLP-1-based therapies for metabolic diseases toward durable efficacy.

Keywords: gene therapy, pancreas, adeno-associated virus, GLP-1

Abbreviations (Up To Five): i.p., intraperitoneal injection; s.c., subcutaneous injection; GLP-1, glucagon-like peptide-1; AAV, adeno-associated virus; VG, vector genomes

Funding Disclosure: Alice Liou Fitzpatrick, Suya Wang, Emily Cozzi, Jay Caplan, Timothy Kieffer, and Harith Rajagopalan are employees and shareholders of Fractyl Health, Inc. Randy Seeley has received research support from and served as a paid consultant for Fractyl Health, Inc.

Conflict Of Interest: Alice Liou Fitzpatrick, Suya Wang, Emily Cozzi, Jay Caplan, Timothy Kieffer, and Harith Rajagopalan are employees and shareholders of Fractyl Health, Inc. Randy Seeley has received research support from Novo Nordisk, Fractyl Health, Astra Zeneca, Congruence Therapeutics, and Eli Lilly; has served as a paid consultant for Novo Nordisk, Eli Lilly, CinRx, Fractyl Health, Structure Therapeutics, and Congruence Therapeutics; and has equity in Calibrate, Rewind, and Levator Therapeutics.

Ethical Approval Disclosure: The animal studies were conducted at Gubra. The animal facility at Gubra is a fully AAALAC accredited unit, and all animal experiments are conducted in accordance with Gubra's bioethical guidelines, which are fully compliant to internationally accepted principles for the care and use of laboratory animals. All experiments are licensed by the Danish Animal Experimentation Council

0088

BMF-219: A Novel Therapeutic Agent to Reestablish Functional Beta Cells and Provide Long-term Glycemic Control

Authors
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Biomea Fusion

Abstract
Background: Inhibition of menin drives an increase in beta-cell proliferation and function. BMF-219, an oral menin inhibitor, is being developed to manage diabetes. Herein we summarize BMF-219 ex-vivo human islet and T2D clinical data.

Methods: BMF-219 was evaluated in ex-vivo human islet cultures to assess beta-cell function and proliferation. In T2D, a randomized, double-blind, placebo-controlled study is ongoing. We report patients treated with BMF-219 100mg QD for 4 weeks, followed until Week 26. Endpoints include glycemic efficacy and safety.

Results: With human islet microtissues cultured for 2-3 weeks under high glucose conditions, BMF-219 increased the fraction of proliferating beta cells resulting in an increase in insulin content and glucose-stimulated insulin secretion. Gene expression changes with CCNA2 and PbK were observed, supporting beta cell proliferation, consistent with published data.
Twenty T2D patients received BMF-219 100mg QD for 4 weeks (with or without food). A reduction in HbA1C of 0.5% or greater was seen in 50% patients at Week 4, which improved to 60% at Week 12. A sustained reduction ≥0.5% was seen in 40% patients at Week 26. At this timepoint, 20% of patients experienced ≥1% HbA1c reduction, with a maximum reduction of 2.5%. BMF-219 was well tolerated (no SAEs or dose discontinuations).

Conclusions: In ex-vivo cultured islets, BMF-219 improved human beta-cell function and proliferation. In T2D, BMF-219 for 4 weeks resulted in meaningful HbA1c reductions at treatment completion (Week 4) and during the 26-week follow-up. Combined results support BMF-219 mechanism of action of beta-cell preservation, reactivation, and proliferation.

Keywords: beta cell, menin, diabetes, BMF-219, islet

Abbreviations (Up To Five): T2D (Type 2 diabetes), QD (Once daily)

Funding Disclosure: Biomea Fusion

Conflict Of Interest: All authors employed by and stock holders of Biomea Fusion

Ethical Approval Disclosure: All authors employed by and stock holders of Biomea Fusion

0023

A Phase II, Randomized, Double-blind, Placebo-controlled, Dose-finding Study of Survodutide (BI 456906) in People Living with Overweight/Obesity

Authors

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Abstract

Background: Survodutide is a dual agonist that acts on GCGR (glucagon receptor), to increase energy expenditure, and the glucagon-like peptide-1 receptor, and may improve therapeutic efficacy.

Aim: This dose-finding study evaluated the efficacy and safety of survodutide in participants with overweight/obesity.

Materials and methods: In this Phase II, double-blind, placebo-controlled study, adults with BMI ≥27 kg/m2 and without diabetes were randomized 1:1:1:1:1 to weekly subcutaneous survodutide (four dose groups: 0.6, 2.4, 3.6, 4.8 mg) or placebo. The 46-week treatment period comprised a 20-week dose escalation phase (increases every 2 weeks), plus a 26-week maintenance phase (fixed dose). The primary endpoint was bodyweight change (%) from baseline at Week 46 to characterize the dose-response relationship for survodutide. A mixed model for repeated measurements was used for analysis.

Results: 387 participants were randomized; treated set, N=386; full analysis set (FAS), N=384; n≈77 per arm. Baseline demographics and clinical characteristics were similar between study arms (FAS): 68.2% female, 78.4% White, mean(SD) age 49.1(12.9) years, BMI 37.1(6.1) kg/m2, bodyweight 105.7(20.4) kg, waist circumference 113.4(14.5) cm, systolic BP 125.6(13.4) mmHg and diastolic BP 81.3(7.8) mmHg. At Week 46, survodutide yielded substantial placebo-corrected reductions from baseline in absolute bodyweight and waist circumference (greatest mean reductions with 4.8 mg survodutide; −15.8 kg and −12.1 cm, respectively) and BP (greatest mean reductions were −6.2 mmHg for systolic BP [3.6 and 4.8 mg survodutide] and −2.9 mmHg for diastolic BP [4.8 mg survodutide]).

Conclusion: Over 46 weeks, survodutide doses ≥2.4 mg substantially improved cardiometabolic outcomes in participants with overweight/obesity.

Keywords: Incretin-based therapies, glucagon receptor, glucagon-like peptide-1 receptor, survodutide, obesity.

Abbreviation: BMI, body mass index; BP, blood pressure; FAS, full analysis set; GCGR, glucagon receptor

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K. J. Lucas declares no conflicts of interest.

E. Startseva, A. Unseld and L. Borowska are employees of Boehringer Ingelheim.

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Ethical approval: n/a

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