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ADA 82ND SCIENTIFIC SESSIONS New Orleans, 2022

Presents

AMERICAN DIABETES ASSOCIATION

82nd SCIENTIFIC SESSIONS

DAILY COVERAGE

TOP 7 SESSIONS: DAY–5

TOPIC OF CONTENT

SESSION-1 :
Machine Learning in Diabetes

Deep Immune Phenotyping of Type 1 Diabetes by Machine Learning

Tuesday, 7th June 2022

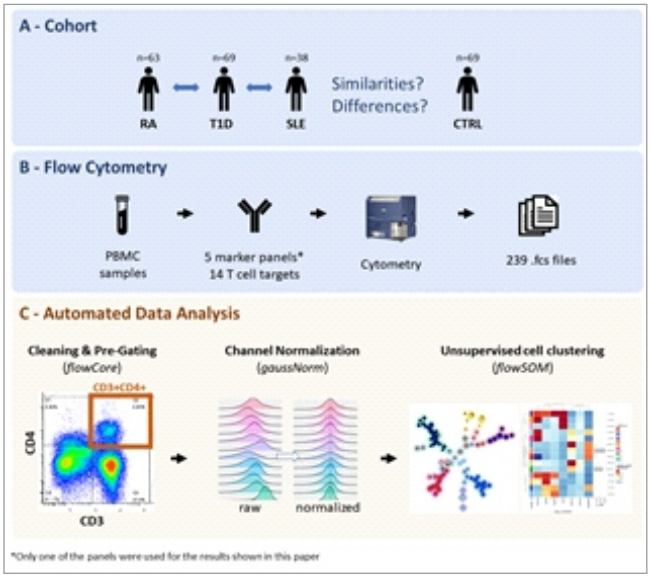
This paper was presented by Drs. Osé Antonio Vera-Ramos, Barbara Prietl, from Graz, Austria, as a part of the symposium "Machine Learning in Diabetes" on Tuesday June 7th 2022 at the 82nd Scientific Sessions of the American Diabetes Association held in New Orleans.

Breakdown of self-tolerance is an important common mechanism in autoimmunity. "We use machine learning (ML) to identify common patterns and dissimilarities between type 1 diabetes (T1D), rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) based on immune phenotyping. PBMCs were isolated from patients with T1D, RA, SLE, and controls."

A FACS approach was applied, and a traditional analysis was compared to a ML method implemented on R and based on self-organizing maps (Fig). Our pipeline includes unsupervised pre-gating, normalization, FlowSOM clustering, and a statistical model (GLMM), to check for significant differential abundances of cell populations among the autoimmune conditions. After applying our automated workflow to one T cell panel we could identify 14 new cell clusters present in all the samples.

The GLMM test revealed a cluster with a significant difference ($p=0.035$) and a trending one ($p=0.059$) on the abundance across the different diseases. In particular, $CD4^{pos}$ T cells expressing high IL-7 receptor (CD127) levels and median amounts of CD15s but low CD25, CD161 and FoxP3 are increased in T1D whereas $CD4^{+}CD25^{++}CD15s^{+}FoxP3^{low}CD161^{low}CD45RA^{-}$ cells are increased in SLE.

In conclusion, our ML workflow identifies a new subtype of T cells significantly increased in T1D. This unsupervised analysis approach for large datasets enables the discovery of new biomarkers complementing traditional workflows.



Machine Learning for Metabolite Estimation to Examine Contributors to Glucose Homeostasis and Adiposity: The GUARDIAN Consortium

Tuesday, 7th June 2022

This paper was presented by Drs. Hannah C. Ainsworth, Xiuqing Guo, Adrienne W. Mackay, from Santa Monica, CA, Winston-Salem, NC, as a part of the symposium "Machine Learning in Diabetes" on Tuesday June 7th 2022 at the 82nd Scientific Sessions of the American Diabetes Association held in New Orleans.

Diabetes is characterized by metabolic dysregulation. Metabolomics captures interactions of cellular processes and environmental exposures to promote disease and can improve mechanistic understanding to identify clinically relevant targets. However, use is limited by cost and sample availability.

To facilitate investigation, machine learning approaches were used in the Insulin Resistance Atherosclerosis Family Study (n=943 Mexican Americans) with empiric metabolites (Metabolon HD4) and GWAS data to generate genetically regulated metabolite estimation models for broad application. 950 metabolites were heritable. Ridge and LASSO regression had cross validated correlation >0.1 for 448 metabolites. In an independent set, LASSO (enforcing sparsity) outperformed Ridge (full polygenic architecture) regression.

Estimation was extended to the GUARDIAN Consortium (n~4377) to assess the association of genetically predicted metabolites with glucose homeostasis and adiposity. Multiple associations (FDR P<0.05) were observed. For glucose homeostasis, mannose, which predicts diabetes development, was inversely associated with glucose effectiveness (P=7.1E-3). For adiposity, urate was positively associated with BMI and waist circumference, capturing lifestyle contributions. In addition, three uncharacterized metabolites were associated with measures of adiposity (P=0.014-3.1E-6) suggesting this approach could contribute to metabolite characterization.

In conclusion, we have developed algorithms for estimating 448 metabolites using genetic data that had good performance in an independent dataset. Estimation models were used to assess association with glucose homeostasis and adiposity highlighting known and novel associations and demonstrating utility. Future work will expand genetic coverage to include rare variants and phenotypic associations to further characterize metabolic dysregulation.

Machine Learning Framework Predicts Metabolic Subphenotypes Using Glucose Dynamics During Oral Glucose Tolerance Test

Tuesday, 7th June 2022

This paper was presented by Drs. Ahmed A. Metwally, Dalia Perelman, Heyjun Park, from Stanford, CA, as a part of the symposium "Machine Learning in Diabetes" on Tuesday June 7th 2022 at the 82nd Scientific Sessions of the American Diabetes Association held in New Orleans.

Type 2 diabetes (T2D) is classically defined by measures of glycemia which do not take into account its physiologic basis, which differs between individuals. Defining the relative contribution of fundamental physiologic processes to glucose dysregulation would facilitate targeted treatment approaches for diabetes prevention and treatment.

"We propose that muscle insulin resistance, beta cell dysfunction, incretin defect, and hepatic insulin resistance are present to varying degrees in individuals predisposed to T2D, who can be thus classified according to their metabolic subphenotype. While this transformative approach to T2D is appealing, traditional metabolic tests are invasive and unavailable outside research units. We tested the ability of the shape of the glucose response curve during an oral glucose tolerance test (OGTT) to identify metabolic subphenotypes. 32 participants underwent gold-standard metabolic tests including frequently-sampled 3-hour OGTT, isoglycemic intravenous glucose infusion for quantification of incretin effect, steady-state plasma glucose measurement of insulin resistance, and calculated hepatic insulin resistance."

"We developed a machine learning framework to predict metabolic subphenotypes of an individual using dynamic features of the glucose time series during the OGTT. Metabolic testing revealed extensive inter-individual heterogeneity and the existence of four major metabolic subphenotypes. The features of the glucose time series identified insulin resistance, beta cell deficiency, and incretin deficiency with auROCs of 94%, 76%, and 75%, respectively. These were superior to standard clinical and laboratory measures of metabolic phenotypes.

We suggest that identification of distinct metabolic subphenotypes using features of the glucose time series during OGTT may both enhance early identification of at-risk individuals as well as inform targeted therapeutic approaches to prevent and treat T2D."

SESSION-2 : Novel Mechanisms of Diabetic Kidney Disease

Intermittent Hypoxia Increased the Expression of DBH and PNMT in Neuronal Cells Via MicroRNA-Mediated Mechanism

Tuesday, 7th June 2022

This paper was presented by Drs. Hin Takasawa, Ryogo Shobatake, Yoshinori Takeda, from Kashihara, Japan, as a part of the symposium "Novel Mechanisms of Diabetic Kidney Disease" on Tuesday June 7th 2022 at the 82nd Scientific Sessions of the American Diabetes Association held in New Orleans.

Sleep apnea syndrome (SAS), characterized by recurrent episodes of oxygen desaturation and reoxygenation (intermittent hypoxia [IH]), is a risk factor for hypertension and insulin resistance.

"We have reported correlation between IH and insulin resistance. However, why hypertension is induced by IH has been elusive. Here, we investigated the effect of IH on the expression of catecholamine metabolizing enzymes using in vitro IH system. Human and mouse neuronal cells, NB-1 and Neuro-2a, were exposed to IH (70 cycles of 5 min hypoxia [1% O2] and 10 min normoxia [21% O2]) or normoxia for 24 hours."

Real-time RT-PCR revealed that IH significantly increased the mRNA levels of dopamine β-hydroxylase (DBH) and phenylethanolamine N-methyltransferase (PNMT) in both NB-1 ($P=0.0271$ and $P<0.0001$, respectively) and Neuro-2a ($P=0.0135$ and $P=0.0341$, respectively). Western blot showed that the expression of DBH and PNMT in the NB-1 cells significantly increased by IH ($P=0.0296$ and $P=0.0007$, respectively). We next prepared reporter plasmids containing human DBH (-1018~+10) and PNMT (-600~+67) upstream of luciferase reporter gene and transfected them into NB-1 cells.

The promoter activities of these genes were not increased by IH. Target mRNA search of microRNA (miR)s using MicroRNA.org program revealed that the mRNAs have a potential target sequence for miR-375. The miR-375 level of IH-treated cells was significantly decreased than that of normoxia-treated cells ($P=0.0222$).

To clarify the role of miR-375, miR-375 mimic and non-specific control RNA (miR-375 mimic NC) were introduced into NB-1 cells. The IH-induced up-regulation of mRNAs of DBH and PNMT was abolished by introduction of miR-375 mimic but not by miR-375 mimic NC. These results strongly suggest that IH stress down-regulates the miR-375 in neuronal cells, resulting in the increased levels of DBH and

PNMT via the inhibition of the miR-375-mediated mRNA degradation, leading SAS patients to hypertension.

Lipotoxicity-Induced Liver Cell Injury Is Prevented by a Novel Positive Allosteric Modulator of the GABAA Receptor

Tuesday, 7th June 2022

This paper was presented by Drs. Lisabeth Rohbeck, Alejandra Romero, Birgit Knebel, Bengt-Frederik Belgardt, Michael Roden, Tania Romacho, Jürgen Eckel from Düsseldorf, Germany, as a part of the symposium "Novel Mechanisms of Diabetic Kidney Disease" on Tuesday June 7th 2022 at the 82nd Scientific Sessions of the American Diabetes Association held in New Orleans.

NAFLD is a highly prevalent condition currently lacking an approved pharmacological therapy. GABA, besides being a neurotransmitter, has been proposed to protect from liver toxicity in both in vivo an in vitro models. We aimed to determine if a novel positive allosteric modulator (PAM) of the GABAA receptor, the thioacrylamide-derivative HK4 which is devoid of blood brain barrier penetration, can protect human hepatocytes against lipotoxicity-induced injury.

Patch clamping in HEK-293 cells and calcium influx measurements in INS-1E cells proved HK4 as a selective PAM of the GABAA receptor. The expression of several main GABAA receptor subunits (α1, α3, α5, β2/3 and γ2) was demonstrated by Western blotting of HepG2 cells. Next generation sequencing was performed and an effect of HK4 on the gene expression profile in response to palmitate was observed. A preventive effect of HK4 on palmitate-induced apoptosis was demonstrated by reduced caspase 3/7 activity both in HepG2 (47.32 ± 6.92% vs. 1065 ± 98.68 %) and human primary hepatocytes (57.13 ± 21.47 % vs. 155.1 ± 3.78 %). This effect was further confirmed by the TUNEL assay (6.41 ± 1.42 % vs. 11.62 ± 0.99 % TUNEL positive cells). This anti-apoptotic effect was mediated through reduced protein expression of cleaved PARP-1, reduced phosphorylation of NF-κB, and by upregulation of the ER chaperone PDI, as measured by Western blotting.

In conclusion, GABAergic signaling reduces lipotoxic-induced apoptosis in hepatocytes by preventing inflammation, DNA damage and ER stress. Therefore, we propose that HK4 may arise as an innovative pharmacological tool to treat or prevent NASH as a first-in-class drug.

SESSION-3: With the Eyes to Future: A 2022 View of DPN Opportunities

The Beneficial Effect of Fenofibrate on Diabetic Retinopathy Is Influenced by PPARA Genetic Variability and Is Mediated by An Increase in FGF21 Levels

Tuesday, 7th June 2022

This paper was presented by Drs. Hetal Shah, Yaling Tang, Christine Mendonca, Jenny Marie Jobe, Josyf Mychaleckyj, Alessandro Doria from Padova, Italy, Boston, MA, Charlottesville, VA, as a part of the symposium "With the Eyes to Future: A 2022 View of DPN Opportunities" on Tuesday June 7th 2022 at the 82nd Scientific Sessions of the American Diabetes Association held in New Orleans.

A PPARA genetic variant (rs6008845) influences the cardiovascular effectiveness of the PPAR-alpha agonist fenofibrate independent of changes in lipid profile. Here we investigated whether the same variant influences fenofibrate effectiveness on diabetic retinopathy (DR).

This was evaluated with regard to DR progression in 592 subjects with prior DR history from the ACCORD Eye Study, and with regard to other pre-specified diabetic eye outcomes in the ACCORD Lipid Study (n=3,650). The effect of fenofibrate on 93 inflammatory biomarkers was studied in 320 rs6008845 T/T homozygotes from ACCORD Lipid and a large retina-eQTL dataset (GtExEye) was used to evaluate the association between rs6008845 and PPARA expression and derive a Genetic Score (eQtGS) of PPARA expression in the retina. rs6008845 modulated fenofibrate effectiveness on DR progression in a way similar to that previously reported for MACE, with the largest benefit being in rs6008845 T/T (OR 0.10, 95% C.I. 0.02-0.74) and the smallest (OR 0.54, 95% C.I. 0.21-1.42) in C/C homozygotes (p for interaction = 0.01). The same synergism was found for severe vision loss (p=0.03). The T allele was associated with higher PPARA retinal expression ($P=4x10^{-38}$) in GtExEye, and ACCORD subjects with higher eQtGS for PPARA expression had better response to fenofibrate on DR progression (P=0.008). Among T/T homozygotes, fenofibrate caused a marked increase in serum FGF21 (+0.87 S.D.; 95% C.I. 0.67-1.07, $P=10x10^{-13}$). Each S.D. increase in log2 FGF21 was associated with a 45% lower risk of severe vision loss (HR 0.55; 95%C.I. 0.34-0.91, p=0.01), explaining 90% of fenofibrate benefit on this outcome in T/T subjects (p=0.03).

In conclusion, fenofibrate effectiveness on DR depends on genetic variants affecting PPARA expression and is mediated by an increase in serum FGF21 - a metabolic and anti-inflammatory cytokine that may therefore be a therapeutic target to treat diabetic eye disease.

Risk Factors of Retinal Oxygen Metabolism and Hemodynamics for Retinopathy in Diabetes

Tuesday, 7th June 2022

This paper was presented By Drs. ZI JIN, ZIXIA ZHOU, BIN ZHANG, FEI WANG, JIABAO CHEN, from Shenzhen, China, Baoding, China as a part of the symposium "With the Eyes to Future: A 2022 View of DPN Opportunities" on Tuesday June 7th 2022 at the 82nd Scientific Sessions of the American Diabetes Association held in New Orleans.

Alterations in retinal oxygen metabolism and hemodynamics are signs of impending diabetic retinopathy (DR). The study aimed to investigate risk factors of the retinal oxygen metabolism and hemodynamics for non-proliferative DR (NPDR).

The study included 166 eyes from 50 age-matched healthy subjects, 80 diabetic patients without DR (Non-DR), and 36 NPDR. Each subjects underwent basic medical history and dilated fundal examinations including color fundus photography, and custom-built multimodal ophthalmic device with function of retinal oximetry and laser speckle flowgraphy. Retinal metabolism was evaluated by retinal arteriolar (SO2a), and venular (SO2v) oxygen saturation, while retinal hemodynamics was evaluated by related parameters such as diastolic duration, flow acceleration index (FAI) and resistance index (RI).

Continuous variables were analyzed by one-way analysis of variance, and categorical variables were analyzed by the chi-square test for three groups. The logistic regression model was used to obtain the risk factors of Non-DR developing into NPDR.

Result: The SO2a and SO2v of NPDR and Non-DR were higher significantly than controls

(p<0.05). There was significant difference among three groups in hemodynamics parameters, including diastolic duration, FAI, blowout score, and RI. The greatest risk factors of Non-DR developing into NPDR descending order were higher RI (odds ratio (OR)=5.84, 95% confidence interval (CI)=1.32-25.78), shorter diastolic duration (OR= 3.46, 95% CI=1.35-8.87), higher glycosylated hemoglobin A1c (OR=1.82, 95% CI=1.15-2.88), lower body mass index (OR=1.74, 95% CI=1.19-2.55), longer duration of diabetic mellitus (OR=1.21, 95% CI=1.05-1.39), smaller age (OR=1.17, 95% CI=1.04-1.32), higher SO2v (OR=1.16, 95% CI=1.00-1.34), higher systolic blood pressure (OR=1.05, 95% CI=1.00-1.10).

Both NPDR and Non-DR show abnormality in retinal oxygen metabolism and hemodynamics. Diastolic duration, RI, and SO2v are independent risk factors in NPDR.

Identifying Blood Biomarkers for Type 2 Diabetes Subtyping: A Report from the ORIGIN Trial

Tuesday, 7th June 2022

This paper was presented by Drs. Hertzel C. Gerstein, Leif Groop, Sibylle Hess, Guillaume Pare from Hamilton, ON, Canada, Helsinki, Finland, Frankfurt, Germany, as a part of the symposium "With the Eyes to Future: A 2022 View of DPN Opportunities" on Tuesday June 7th 2022 at the 82nd Scientific Sessions of the American Diabetes Association held in New Orleans.

Diabetes (DM) can be classified into 5 subtypes characterized by distinct progression in dysglycaemia and complications. Using 5 clinical variables, we categorized 7017 participants from the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial into 1/auto-immune DM (n=241), 2/insulin-deficient DM (n=1594), 3/insulin-resistant DM

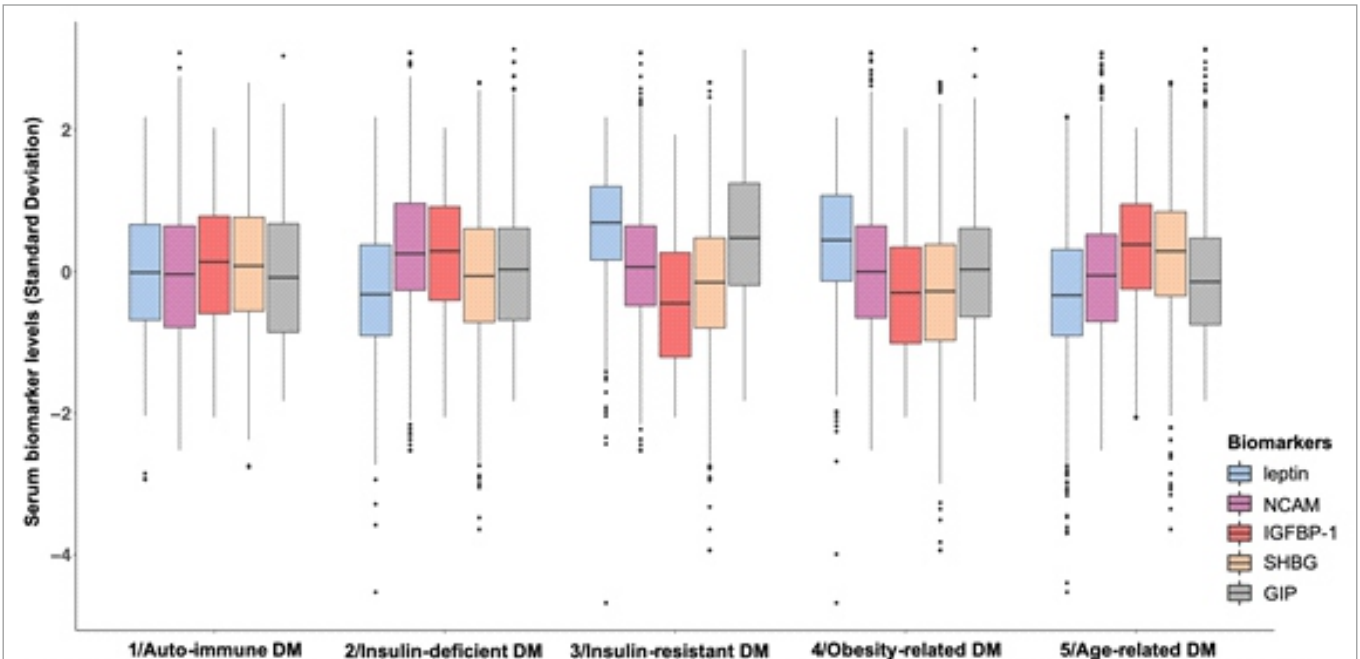


Figure: Baseline blood levels of identified biomarkers in each of the five diabetes subtypes in ORIGIN. Boxplots represent the median and second and third quartiles; error bars represent the 95% confidence interval.

(n=914), 4/obesity-related DM (n=1595), 5/age-related DM (n=2673). Yet, whether blood biomarkers are associated with these subtypes is unknown. Forward-selection logistic regression models were used to identify biomarkers that were each independent determinant of one cluster versus the others, among 233 selected cardiometabolic proteins measured at baseline.

Models were adjusted for age, sex, ethnicity, C-peptide level, diabetes duration. A total of 13, 2, 7 and 10 biomarkers were independent determinants of DM subtypes 2 to 5 respectively (all $P<4.3x10^{-5}$). A combination of 5 biomarkers that were distinctively associated with clusters (fig), showed a diagnosis performance, through AUC-ROC curves, of 0.71, 0.86, 0.88, 0.82 to respectively distinguish cluster 2 to 5 from the others. No biomarkers other than GAD antibodies were determinants of cluster 1. We identified 5 serum biomarkers, as independent determinants of DM subtypes, that could be used as a diagnosis test for DM subtyping. Although this requires further validation in an independent population.

SESSION-4:
Future of Diabetes: The Next Frontier with Dual Incretin

Glycemic Control with Tirzepatide in People with Type 2 Diabetes by Baseline HbA1c =8.5% or >8.5%

Tuesday, 7th June 2022

This paper was presented by Drs. Grazia Aleppo, Christophe De Block, Joshua A. Levine, Elisa Gomez-Valderas, Brian D. Benneyworth, from Chicago, IL, Edegem, Belgium, Indianapolis, IN, as a part of the symposium "Future of Diabetes: The Next Frontier with Dual Incretin" on Tuesday June 7th 2022 at the 82nd Scientific Sessions of the American Diabetes Association held in New Orleans.

Tirzepatide, a once weekly GIP/GLP-1 receptor agonist in development for T2D, demonstrated superior glycemic control in the Phase 3 SURPASS clinical trial program. This post-hoc analysis assessed glycemic control with tirzepatide in participants stratified by baseline (BL) HbA1c (≤8.5%, >8.5%).

Mean change from BL in HbA1c was assessed in tirzepatide-treated participants (5, 10 or 15 mg) from SURPASS-1 (monotherapy), SURPASS-2 (add-on to MET), SURPASS-3 (add on to MET ± SGLT2i), SURPASS-4 (add-on to MET, SGLT2i, or sulfonylurea) and SURPASS-5 (add-on to insulin glargine ± MET) at trial endpoints (40 or 52 weeks). Safety was also presented. Treatment comparisons were estimated using data while participants were on treatment and without rescue medications (efficacy estimand).

Across each SURPASS trial, ranges in mean BL HbA1c were 7.94-8.52%, mean BMI were 31.9-34.2 kg/m2 and mean diabetes duration were 4.7-13.3 years. At trial endpoints, HbA1c reductions from BL ranged from 1.55-2.14% in the BL HbA1c ≤8.5% subgroup and 2.70-3.46% in the BL HbA1c >8.5% subgroup (Table). Gastrointestinal side effects were similar to those reported in the incretin class and hypoglycemic events (blood glucose <54 mg/dL or severe) were low.

In conclusion, significant and clinically meaningful HbA1c reductions were observed with tirzepatide, irrespective of BL HbA1c.

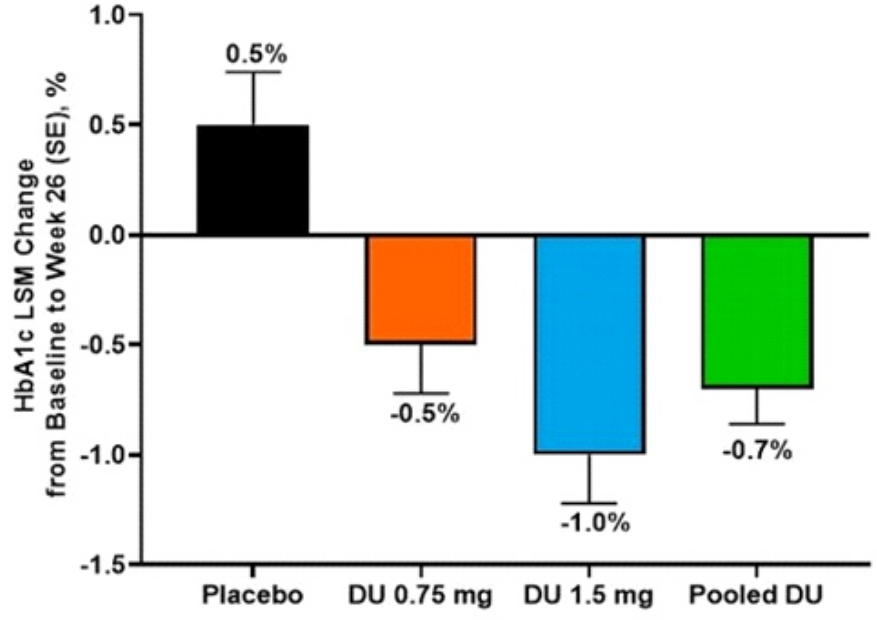
Dulaglutide in Youth with Type 2 Diabetes (T2D) – Results of the AWARD-PEDS Randomized, Placebo-Controlled Trial

Tuesday, 7th June 2022

This paper was presented by Drs. Silva A. Arslanian, Jang Ik Cho, Tamara S. Hannon, from Pittsburgh, PA, Indianapolis, IN, Aurora, CO, as a part of the symposium "Future of Diabetes: The Next Frontier with Dual Incretin" on Tuesday June 7th 2022 at the 82nd Scientific Sessions of the American Diabetes Association held in New Orleans.

AWARD-PEDS was a Phase 3 trial to assess the efficacy and safety of dulaglutide (DU), a once-weekly GLP-1 receptor agonist, in youth (10 to <18 years old) with T2D treated with lifestyle alone or on stable metformin with or without basal insulin. Participants (mean age, 14.5 yrs; mean BMI, 34.1 kg/m^2) were randomized to placebo (N=51), DU 0.75 mg (N=51), or DU 1.5 mg (N=52).

The primary aim was to demonstrate superiority of DU (pooled doses) vs. placebo for change in HbA1c at 26 weeks. Analyses included all patients with ≥1 dose of study drug, excluding data after initiation of rescue therapy. DU was superior to placebo (figure) in improving glycemic control measured by change in HbA1c, percent of patients with HbA1c <7%, and change in fasting glucose at



HbA1c ETD vs placebo:		-1.0%	-1.5%	-1.3%
95% CI:		-1.7, -0.4	-2.2, -0.9	-1.8, -0.7
p-value:		.002	<.001	<.001
% patients HbA1c <7%:	18.4%	60.0%	53.2%	56.5%
p-value:		<.001	<.001	<.001
FPG LSM change, mg/dL:	17.3	-8.5	-27.8	-18.6
p-value:		0.021	<.001	<.001

ETD, estimated treatment difference; DU, dulaglutide; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; LSM, least-squares mean; SE, standard error. Analyses included all patients receiving at least 1 dose of study drug, excluding data after rescue therapy. Change from baseline is from MMRM; % patients with HbA1c<7% is from longitudinal logistic regression.

Week 26. No effect of DU was observed on BMI change (p=0.776). Fewer patients assigned to DU compared to placebo required rescue therapy (2.9% vs. 17.6% respectively, p=0.003). Incidence of common GI adverse events was higher in DU group vs. placebo [nausea (14.6% vs. 7.8%), vomiting (15.5% vs. 3.9%), diarrhea (18.4% vs. 13.7%)] but comparable to that observed in adults.

In conclusion, in youth with inadequately controlled T2D treated with or without metformin and/or basal insulin, once weekly DU 0.75 mg or 1.5 mg was superior to placebo in improving glycemic control without an effect on BMI through 26 weeks, with a safety profile consistent with that established in adults.

Low Incretin Effect Is Associated with Longitudinal Decline of Beta-Cell Function and Insulin Sensitivity in Obese Youth

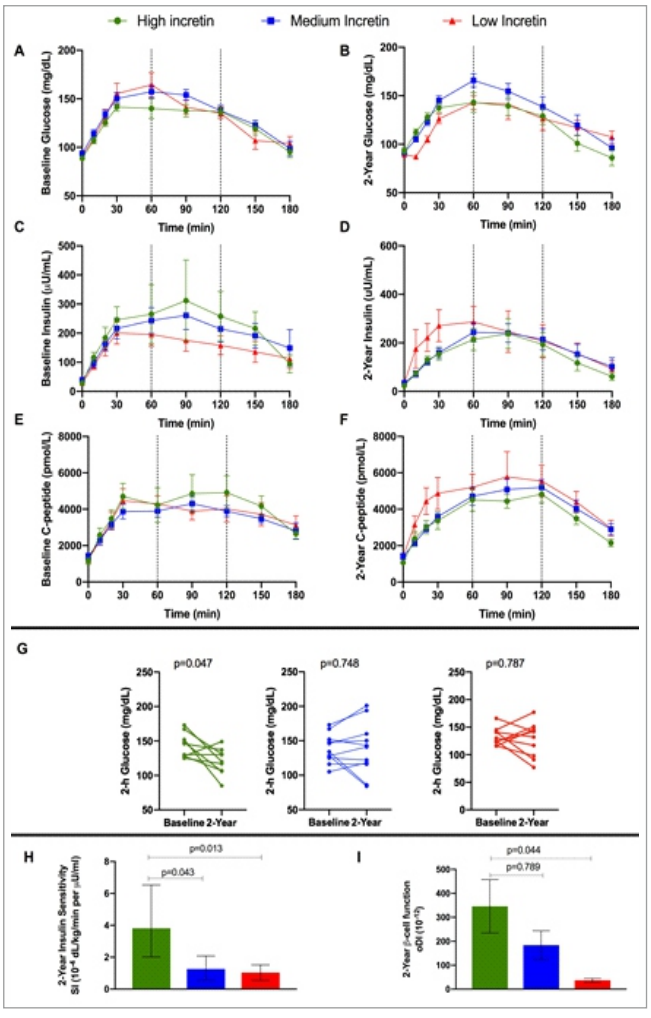
Tuesday, 7th June 2022

This paper was presented by Drs. Alfonso Galderisi, Jessica O. Lat, Stephanie Samuels, Bridget Pierpont, Michelle A. Van Name, Nicola Santoro, Sonia Caprio, from Padova, Italy, New Haven, CT, as a part of the symposium "Future of Diabetes: The Next Frontier with Dual Incretin" on Tuesday June 7th 2022 at the 82nd Scientific Sessions of the American Diabetes Association held in New Orleans.

We assessed the longitudinal trajectory of beta-cell function with respect to baseline incretin effect in youth with obesity.

At baseline and two years, youth with obesity and 2-h glucose ≥ 120mg/dL underwent a 3-hour OGTT and isoglycemic intravenous glucose infusion (to quantify the incretin effect). Participants were stratified into three tertiles based on the baseline incretin effect. The oral minimal model quantified beta cell function (oDI) and insulin sensitivity (SI).

Thirty participants completed the assessments [follow-up: age 18.6±2.4y, 19F; BMI 38.6±7.4 kg/m^2, NGT/IGT/T2D 12/17/1]. At 2 years, 2-h glucose improved in the high incretin group (p=0.047), but was stable in the middle- and low- incretin groups (panel G). At 2 years, the baseline high-incretin group exhibited a lower 60-min glucose (p=0.026) than the low-incretin group, with similar 120-min glucose (p=0.696), despite the low-incretin cohort's relative increase in early insulin secretion (panel D, F). The low-incretin tertile also exhibited a reduced β-cell function (oDI) at follow-up (panel I) (p=0.044) mainly due to lower insulin sensitivity (panel H) (p=0.013).



Conclusion: Low incretin effect is associated with a longitudinal decline of beta cell function and decreased insulin sensitivity, despite greater first-phase insulin secretion.

SESSION-5: The Future of Insulin: Weekly, Oral, Smart or Interchangeable Therapies

Hypoglycemia Frequency and Physiological Response to Double or Triple Doses of Once-Weekly Insulin Icodec vs. Once-Daily Insulin Glargine in T2D

Tuesday, 7th June 2022

This paper was presented by Drs. Eva Svehlikova, Kristine Niss Arfelt, Roman Cailleteau, from Aalborg, Denmark, Graz, Austria, Søborg, Denmark, as a part of the symposium "The Future of Insulin: Weekly, Oral, Smart or Interchangeable Therapies" on Tuesday June 7th 2022 at the 82nd Scientific Sessions of the American Diabetes Association held in New Orleans.

Insulin icodec is a basal insulin in development for once-weekly (OW) dosing. The aim of this study was to compare the hypoglycemia frequency and response after icodec vs. insulin glargine U100 (IGlar) overdosing. In a randomized, open-label, two-period crossover trial, 43 individuals with T2D on basal insulin±metformin (mean±SD age 56±9 yrs, HbA1c 7.2±0.7%) received OW icodec for 6 weeks and once-daily IGlar for 12 days at equimolar total weekly doses based on the individual daily run-in IGlar dose (mean 30±14 U) titrated to a fasting SMPG target of 80-130 mg/dL. Once at steady state, double (DD) and triple (TD) doses of icodec and IGlar were followed by hypoglycemia induction 44 h (icodec) or 7 h (IGlar) post-dose (expected time of maximum glucose-lowering effect).

First, euglycemia was maintained at 100 mg/dL by variable i.v. glucose. Then, PG was allowed to decrease to a nadir of no less than 45 mg/dL maintained for 15 min. Euglycemia was restored by constant i.v. glucose. Hypoglycemic symptom score (HSS) and counterregulatory hormones were assessed at PG 100 mg/dL and at predefined PG levels until nadir PG. For DD, clinically significant hypoglycemia (PG<54 mg/dL) occurred in 40 vs. 36% of subjects for icodec vs. IGlar (odds ratio 1.28; p=0.63).

For TD, clinically significant hypoglycemia occurred in 53 vs. 70% of subjects (odds ratio 0.48; p=0.14), mean nadir PG was 56 vs. 52 mg/dL (treatment ratio 1.07; p<0.001), change in HSS at nadir PG was comparable for icodec vs. IGlar (treatment difference 0.46; p=0.77), responses in adrenaline, noradrenaline and cortisol during hypoglycemia development were greater for icodec vs. IGlar, while glucagon and growth hormone levels increased similarly.

In conclusion, a DD or TD of once-weekly insulin icodec does not lead to increased risk of hypoglycemia compared to once-daily IGlar. During hypoglycemia, a comparable symptomatic response and a moderately greater endocrine response were seen for icodec vs. Iglar.

Increased Expression of Insulin Signalling Intermediates after Six Months of Metformin Medical Intervention in Women with Obesity and Polycystic Ovary Syndrome

Tuesday, 7th June 2022

This paper was presented by Dr. Stanley Andrisse, Washington, DC, as a part of the symposium "The Future of Insulin: Weekly, Oral, Smart or Interchangeable Therapies" on Tuesday June 7th 2022 at the 82nd Scientific Sessions of the American Diabetes Association held in New Orleans.

We hypothesize that in women experiencing obesity and PCOS, the women with higher levels of free androgen index will display more dysregulation in the insulin signaling pathway in adipose tissue. More specifically, we believe that visceral more than subcutaneous adipose tissue in the women in the study will display more dysregulation; and lastly that bariatric surgery will alleviate insulin signaling dysregulation.

Here, we performed molecular analyses (Western blots and qPRC) exploring the insulin signaling pathway in visceral and subcutaneous (SubQ) adipose tissue from women with obesity and PCOS undergoing RYGB bariatric surgery; and SubQ WAT from women with obesity and PCOS at baseline and six-months after medical intervention with metformin (MTF).

Subcutaneous (SubQ) white adipose tissue (WAT) displayed a trending (p=0.2) but non-significant increase in p-ACC compared to visceral WAT from women with PCOS and obesity pre-bariatric surgery. Six months of MTF increased p-ACC in SubQ WAT by 5-fold compared to zero months (baseline) in women with PCOS and obesity. IR displayed similar expression in the visceral compared to SubQ WAT in women with PCOS and obesity pre-bariatric surgery. IR expression increased by 20-fold at 6-months of MTF compared to baseline in SubQ WAT of women with PCOS and obesity. Phosphorylated forkhead box 01 (p-FOXO1) displayed similar expression in the visceral compared to SubQ WAT in women with PCOS and obesity. However, p-FOXO1 was decreased at 6-months of MTF compared to baseline in women with PCOS and obesity. p-AKT levels were similar in visceral compared to SubQ WAT in women with PCOS and obesity pre-bariatric surgery. However, p-AKT levels were significantly increased by 4-fold at 6-months of MTF compared to 0-months in women with PCOS and obesity. None of the insulin signaling intermediates measured were altered in visceral compared to SubQ in women with obesity and PCOS.

A Comparison of Insulin Glargine U300 and Insulin Degludec Around Spontaneous Exercise Sessions in People with Type 1 Diabetes–The ULTRAFLEXI-1 Study

Tuesday, 7th June 2022

This paper was presented by Drs. Othmar Moser, Alexander Mueller, Felix Aberer, from, Graz, Austria, Bayreuth, Germany as a part of the symposium "The Future of Insulin: Weekly, Oral, Smart or Interchangeable Therapies" on Tuesday June 7th 2022 at the 82nd Scientific Sessions of the American Diabetes Association held in New Orleans.

Regular physical activity and exercise represent a corner stone in the treatment of type 1 diabetes (T1D); however, exercise-induced hypoglycemia remains the major barrier to a physically active lifestyle. Therefore, the ULTRAFLEXI-1 study compared two basal insulin analogues, Glargine 300U/ml (IGlar U300) and Degludec (IDeg), in two different doses (100% and 75% of the regular dose) when used around spontaneous exercise sessions in adults with T1D.

We performed a randomized, single-center, four-period, cross-over trial (EudraCT: 2019-003209-89) and included adults with T1D treated with multiple daily insulin injections and an HbA1c ≤10% (≤86 mmol/mol). In each of the four 2-weeks-periods, participants attended six spontaneous evening cycling sessions (60 minutes, moderate intensity). The days of exercising were randomized and announced at 8 A.M. to the participants. The basal insulin used on the exercise days during the four periods were: IGlar U300 100% or 75% of the regular dose or IDeg 100% or 75%, respectively. 100% of the regular basal insulin dose was used at all non-exercise days. CGM was performed using a blinded Dexcom G6 device. The primary outcome was TBR (<70 mg/dl) during the six 24-hour post-exercise periods in the four trial arms. The difference in TBR between 100% IGlar and 100% IDeg or 75% IGlar and 75% IDeg was analyzed in hierarchical order using the repeated measures linear mixed model.

25 people were enrolled (14 male), aged 41.4±11.9 years, with a mean diabetes duration of 16.8±10.4 years and a mean HbA1c of 7.5±0.8%. (59±9 mmol/mol). Mean TBR during the 24-hour periods following the exercise sessions was 2.71±2.56% for IGlar U300 (100%) and 4.37% ±3.43% for IDeg (100%) (p=0.025) as well as 2.28±2.67% for IGlar U300 compared to 2.55 ±2.87% with IDeg when using the 75% dose on exercise days (p=0.720).

Conclusion: Time spent in hypoglycemia after spontaneous exercise sessions was significantly lower in people with type 1 diabetes receiving IGlar U300 as compared to IDeg when the 100% dose was used.

SESSION-6: Positive Impact of DCESs on Therapeutic Inertia

A Qualitative Study to Understand Why People Living with Obesity and General/Family Practitioners Experience Therapeutic Inertia in Obesity

Tuesday, 7th June 2022

This paper was presented by Drs. David C. Lau, Ian Patton, Reena Lavji, Adel Belloum, from Calgary, AB, Canada, Bowmanville, ON, Canada, as a part of the symposium "Positive Impact of DCESs on Therapeutic Inertia" on Tuesday June 7th 2022 at the 82nd Scientific Sessions of the American Diabetes Association held in New Orleans.

Medical nutrition therapy and physical activity are often used exclusively for obesity treatment despite the availability of effective adjunctive interventions, including psychological intervention, pharmacological therapy, and bariatric surgery. We conducted a qualitative study through interviews with people living with obesity (PwO) and general/family practitioners (GP/FPs) to better understand the factors contributing to healthcare decision-making and therapeutic inertia in obesity management. Phone interviews were conducted by the same investigator using discussion guides informed by the Theoretical

Domains Framework (TDF). Eligibility criteria for PwO included having a BMI over 30 kg/m^2.

A total of 20 PwO and 20 GP/FPs across Canada were interviewed with representation across gender and ethnicity. PwO also varied in obesity classification and experience with management strategies. GP/FPs varied in practice type, local community, and awareness of the 2020 Canadian Adult Obesity Clinical Practice Guidelines.

Themes related to therapeutic inertia mapped to all 14 TDF domains. Both PwO and GP/FPs often perceived obesity to be a secondary health priority that is associated with negative emotions, which had pervasive influence on obesity management. PwO were hesitant to explore new strategies due to financial barriers, access to support, and concerns of adverse side-effects, effectiveness, and sustainability of interventions that support eating and physical activity behavioral changes. GP/FPs were limited in time and resources, and were hesitant to recommend specific treatments due to concerns of risks, effectiveness, and accessibility. GP/FPs were also hesitant to make referrals due to skepticism of whether other healthcare providers can provide better care. Future research will validate these themes in a larger, national sample of PwO and GP/FPs to understand how individuals can overcome the therapeutic inertia.

Development of Predictive Models for Health Care Outcomes of Patients with Chronic Kidney Disease and Type 2 Diabetes

Tuesday, 7th June 2022

This paper was presented by Drs. Richard Sheer, Radhika Nair, Margaret K. Pasquale, from Cedar Park, TX, Cincinnati, OH, Wuppertal, Germany, as a part of the symposium "Positive Impact of DCESs on Therapeutic Inertia" on Tuesday June 7th 2022 at the 82nd Scientific Sessions of the American Diabetes Association held in New Orleans.

Progression of chronic kidney disease (CKD) is associated with increased risk of cardiovascular or renal events that contribute to increasing healthcare costs. The purpose of this study was to develop predictive models for rapid progression of CKD, days out of the home, and high costs for patients with both CKD and type 2 diabetes (T2D).

This retrospective observational cohort study used administrative claims data for patients with CKD (stage 3-4) and T2D aged 65-89 years enrolled in a Humana Medicare Advantage Prescription Drug plan 1/1/2012-12/31/2017. Patients were enrolled >1 year pre-index and followed up to one-year post-index. Outcomes included rapid progression of CKD (>1 decrease in estimated glomerular filtration rate [eGFR] >5 mL/min/1.73m^2 per year), days out of the home (days spent out of their residence [e.g., hospital]; >2% days out of the home) and high costs (75-90th and >90th percentiles) post-index. Pre-index demographic and clinical characteristics, selected based on the LASSO technique, were included in logistic regression models to generate parameter estimates and model performance statistics. We identified 169,876 patients with CKD stage 3-4 and T2D.

The C-statistics for the models ranged from 0.694 to 0.745. Lower initial eGFR led to incrementally higher risk for more days out of the home and high costs. Patients with urinary albumin to creatinine ratio (UACR) >300 mg/g had three times increased risk for rapid progression of CKD, 57% higher risk of more days out of the home, and, among those in the 75-90th cost percentile, had 38% higher costs than patients with UACR<30 mg/g. The presence of congestive heart failure, anemia, or higher pre-index utilization (>5 physician visits) increased the risk for all outcomes. The

predictive models developed in this study can be potentially used as decision support tools for clinicians and payers, and the risk scores from these models can be applied to future outcomes studies focused on patients with T2D and CKD.

SESSION-7: Obesity Management as a Primary Goal: It's Time for a Paradigm Shift

Long-Term Type 2 Diabetes Remission After Bariatric Surgery in Patients with and Without Liver Steatosis

Tuesday, 7th June 2022

This paper was presented by Drs. Anne Lautenbach, Marie Wernecke, Sebastian M. Meyhöfer, Svenja Meyhöfer, Fabian D. Stoll, Jens Aberel, from Hamburg, Germany, Luebeck, Germany, as a part of the symposium "Obesity Management as a Primary Goal: It's Time for a Paradigm Shift" on Tuesday June 7th 2022 at the 82nd Scientific Sessions of the American Diabetes Association held in New Orleans.

Nonalcoholic steatohepatitis (NASH) is considered the hepatic manifestation of insulin resistance. Therefore, we aimed to assess the association between biopsy-proven liver steatosis and long-term remission of type 2 diabetes (T2D) 8 years following different bariatric procedures.

In a retrospective cohort study including 249 patients with and without T2D, the association between biopsy-proven NASH and long-term remission of T2D 8 years following sleeve gastrectomy (SG) and Roux-enY-gastric bypass (RYGB) has been assessed.

Out of 249 patients, 15.3% showed NASH and T2D at the time of surgery. 8 years after surgery, T2D remission was achieved in 44.7% of patients with NASH compared to 76.0% without NASH. Patients with T2D remission were younger, had higher BMI, displayed lower HbA1c and lower preoperative insulin use ($p<0.001$). Patients without remission of T2D showed higher steatosis scores ($p<0.05$). In a multivariate logistic regression, higher preoperative HbA1c (OR 0.41), insulin use (OR 0.16) and preexisting liver fibrosis (OR 0.19) decreased the probability of long-term T2D remission ($p<0.05$). Liver steatosis, hepatocyte ballooning or lobular inflammation were not significantly associated with T2D remission. Patients without T2D were predominantly female, of younger age ($p<0.001$) and displayed lower scores of steatosis, hepatocyte ballooning and lobular inflammation ($p<0.05$). With regard to type of surgery, there was no significant difference in T2D remission.

Our data suggest that long-term remission of T2D after bariatric surgery (BS) is associated with lower preoperative insulin use and lower biopsy-proven steatosis scores in patients with NASH. Furthermore, T2D remission might be less likely in patients with liver fibrosis. Type of surgery did not affect T2D remission. Our results might help identify patients with NAFLD who benefit most from BS with regard to glycemic outcomes long-term.

Glucometabolism Benefited Differently from Bariatric Surgery Within Four Artificial Intelligence–Assisted Metabolic (AIM) Subtypes of Obesity

Tuesday, 7th June 2022

This paper was presented by Drs Yao Liu, Chunjun Sheng, Ziwei Lin, Shen Qui from Shanghai, China, as a part of the symposium "Obesity Management as a Primary Goal: It's Time for a Paradigm Shift" on Tuesday June 7th 2022 at the 82nd Scientific Sessions of the American Diabetes Association held in New Orleans.

The purpose of this study was to look into the benefit of a bariatric surgery in four artificial intelligence-assisted metabolic (AIM) subtypes of obesity with respect to the improvement of glucometabolism, as well as the remission of diabetes and hyperinsulinemia.

Methods: This multicenter retrospective study prospectively collected data from 5 hospitals in China from 2010 to 2021. A total of 1008 patients who underwent a bariatric surgery were enrolled (median age 31 years; median BMI 38.1kg/m^2; 57.40% women) and grouped into four AIM subtypes of obesity. Data at baseline, 3- and 12-months post-surgery were collected for the longitudinal effect analysis.

At baseline, the hypermetabolic obesity-hyperinsulinemia (HMO-I) group was characterized by severe insulin resistance and high incidence of hyperinsulinemia (87.8%). After surgery, HMO-I with hyperinsulinemia had achieved remission, yet the prevalence of hypoglycemia was still high (42.9%). Hypometabolic obesity (LMO) group showed decompensated insulin secretion and high incidence of diabetes (99.2%) at baseline. After surgery, 62.1% of LMO patients with diabetes achieved remission, lower than the other three groups. Still, the bariatric surgery significantly reduced their blood glucose (median HbA1c decreased by 27.2%). For both metabolic healthy obesity (MHO) and hypermetabolic obesity-hyperuricemia (HMO-U) groups, who showed a relatively healthy glucometabolism at baseline, prevalence of glucometabolic comorbidities improved moderately after surgery.

This multicenter study found that the four AIM subtypes of obesity benefited differently from a bariatric surgery in terms of glucometabolism. Bariatric surgery significantly relieves hyperinsulinemia and hyperglycemia for HMO-I and LMO, respectively. As a result, patients of the two subtypes should be motivated for a bariatric surgery for the improvement of glucometabolism.

A Weight Management Program Tailored for Adults with Type 2 Diabetes: Effects on Glycemic Control

Tuesday, 7th June 2022

This paper was presented by Drs. John W. Apolzan, Jessica G. Larose, Stephen D. Anton, from Baton Rouge, LA, Richmond, VA, New York, NY, as a part of the symposium "Obesity Management as a Primary Goal: It's Time for a Paradigm Shift" on Tuesday June 7th 2022 at the 82nd Scientific Sessions of the American Diabetes Association held in New Orleans.

Clinical weight loss interventions improve glycemic control in adults with type 2 diabetes (T2D), but are costly and have limited accessibility. The objective of this trial was to test the efficacy of a diabetes-tailored widely

available weight management program (WW, formerly Weight Watchers) on glycemic control in adults with T2D.

This was a prospective 24-week single arm, three-site clinical trial. Participants (n= 136) had T2D, a baseline HbA1c between 7-11%, and a BMI between 27-50 kg/m^2. All participants received the 24-wk intervention, which consisted of the WW digital + workshop program tailored for people with T2D, and included weekly virtual workshops and use of the WW App. Assessments occurred at baseline, wk 12 (83.8% retention), and wk 24 (83.1%). Primary outcome was change in HbA1c at 24 weeks. Secondary endpoints were changes in body weight and the Diabetes Distress Scale (DDS). Generalized linear effects models were used for statistical analysis (MAR) and used an intent-to-treat analysis.

Participants were 56.8 ± 0.8 y (Mean ± SEM), 80.2% Female, 62.2% non-Hispanic white. Baseline BMI was 36.2±0.6 kg/m^2. Baseline HbA1c, weight, and total DDS score were 7.9±0.1%, 104.3±1.8 kg, and 2.2±0.1, respectively. HbA1c decreased 0.6±0.1% at wk 12 and 0.8±0.1% at wk 24 (both $p < .0001$). Body weight decreased 4.6±0.5% at wk 12 and 5.7±0.5% at wk 24 (both $p < .0001$). Total DDS score decreased 0.2±0.1 at wk 12 and 0.3±0.1 at wk 24 (both $p < .0001$).

The widely available WW program, modified for those with T2D, had favorable and clinically meaningful effects on glycemic control, body weight, and diabetes distress at 12 and 24 weeks.

ADA 82ND SCIENTIFIC SESSIONS New Orleans, 2022

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