

Cardiovascular Outcome Studies

Symmetric and Asymmetric Dimethylarginine as Risk Markers of Cardiovascular Disease, All-Cause Mortality and Deterioration in Kidney Function in Type 2 Diabetes

Emilie Hein Zobel², Bernt Johan von Scholten², Henrik Reinhardt², Frederik Persson², Tom Teerlink¹,
Tine W. Hansen², Hans-Henrik Parving³, Peter K. Jacobsen⁴, Peter Rossing²

¹Department of Clinical Chemistry, VU University Medical Center, Netherlands

²Complications research, Steno Diabetes Center Copenhagen, Denmark

³Department of Endocrinology, Rigshospitalet, University of Copenhagen, Denmark

⁴The Heart Center, Rigshospitalet, University of Copenhagen, Denmark

Background: In the ongoing search for biomarkers that can improve risk prediction in type 2 diabetes symmetric dimethylarginine (SDMA) and asymmetric dimethylarginine (ADMA) are of interest due to their biologic function and promising results in different populations.

Objective: To evaluate SDMA and ADMA as risk markers of cardiovascular disease, all-cause mortality and deterioration in renal function in a well characterised type 2 diabetic population with microalbuminuria and without symptoms of coronary artery disease.

Methods: 200 participants followed for 6.1 years. SDMA and ADMA were measured at baseline. Endpoints included 1) composite cardiovascular endpoint (n=40); 2) all-cause mortality (n=26); and 3) decline in eGFR of 30% (n=42). Cox models were unadjusted and adjusted for traditional risk factors (sex, age, systolic blood pressure, LDL-cholesterol, smoking, HbA_{1c}, creatinine and urinary albumin excretion rate). To assess if SDMA or ADMA improved risk prediction beyond traditional risk factors we calculated c-statistics and relative integrated discrimination improvement (rIDI).

Results: Higher SDMA was associated with increased risk of all three endpoints (unadjusted: $p \leq 0.001$; adjusted: $p \leq 0.02$). Higher ADMA was associated with all-cause mortality (unadjusted: $p = 0.002$; adjusted: $p = 0.006$), but not cardiovascular disease or decline in eGFR ($p \geq 0.29$). The c-statistics was not significant for any of the endpoints for either SDMA or ADMA ($p \geq 0.10$). The rIDI for SDMA was 15.0% ($p = 0.081$) for the cardiovascular endpoint, 52.5% ($p = 0.025$) for all-cause mortality and 48.8% ($p = 0.007$) for decline in eGFR; for ADMA the rIDI was 49.1% ($p = 0.017$) for all-cause mortality.

Conclusion: In persons with type 2 diabetes and microalbuminuria higher SDMA was associated with incident cardiovascular disease, all-cause mortality and deterioration in renal function. Higher ADMA was associated with all-cause mortality. SDMA and ADMA significantly improved risk prediction for all-cause mortality, and SDMA for deterioration in renal function beyond traditional risk factors.

Cardiovascular Outcome Studies

Metabolic Syndrome Risk Factors Changes over a Decade during Menopausal Transition in Tehranian Women: Tehran Lipid and Glucose Study (TLGS)

Elaheh Ainy¹, Golshan Amirshkari², Fatemehe Ramezani Tehrani³, Marzieh Rostami Dovom⁴, Fereidoun Azizi⁵

¹Shahid Beheshti University of Medical Sciences, Research affair, Safety Promotion and Injury Prevention Research Center, Iran

²Shahid Beheshti University of Medical Sciences, Reproductive Endocrinology Research Center, Research Institute for Endocrine Sciences, Iran

³Shahid Beheshti University of Medical Sciences, Reproductive Endocrinology Research Center, Research Institute for Endocrine Sciences, Iran

⁴Shahid Beheshti University of Medical Sciences, Reproductive Endocrinology Research Center, Research Institute for Endocrine Sciences, Iran

⁵Shahid Beheshti University of Medical Sciences, Research Institute for Endocrine Sciences, Iran

Background: Metabolic syndrome is a group of risk factors that raises risk of heart disease, diabetes and stroke.

Objective: This study was conducted to assess the metabolic syndrome (MetS) risk factors changes over a decade during menopausal transition in Tehranian women.

Methods: In a cross sectional study 5884 subjects were selected from 15005 participants of the Tehran Lipid and Glucose cohort Study (TLGS) and assessed for MetS risk factors changes over a decade (2007-2017). 5884 women aged 15–76 years, among all participants of the TLGS, were classified into five groups: 1; normal (women who had menses normally or with drug), 2; Pre-M (menopausal), aged 45-49 years, 3; M (menopausal) with a permanent cessation of menses of 12 months and 3 years, 4; Post-M women who had at least a 3-year history of cessation of menses and 5; 66-76 years. All MetS components were evaluated following age adjustment according to the ATP III criteria.

Results: The mean ages of normal, pre-M, menopausal, post-M and women 66-76 years groups were 30.9±7.9, 46.8±1.4, 53.7±2.3, 57.7±5.5 and 70.4±3.1 years respectively. In studied groups' fasting plasma glucose levels, waist, systolic blood pressure gradually increased (p 0.001). Cholesterol, LDL-c and triglyceride levels, diastolic blood pressure, gradually increased, the highest level was observed in menopausal group then a little downturn was observed in post-M and in women over a decade 66-76 years (p 0.001). There was no significant difference in HDL-c levels. Frequency of MetS was significantly higher in menopausal and women over a decade 66-76 years.

Conclusion: It is concluded that the frequency of MetS is significantly higher in menopausal and women over a decade 66-76 years as compared to other groups. Fasting plasma glucose levels, waist, systolic blood pressure are the most frequent feature in comparison to other factors.

Cardiovascular Outcome Studies

Effects of N-acetyl Cysteine and Melatonin on Early Reperfusion Injury in Patients undergoing Coronary Artery Bypass Grafting: A Randomized, Open-Labelled, Placebo-Controlled Trial

Ali Movahed¹, Afshin Ostovar^{1,2}, Samad Akbarzadeh^{1,3}, Ebrahim Shafiei^{1,4}

¹Biochemistry, Bushehr University of Medical Sciences, Iran

²Social Medicine, The Persian Gulf Tropical Medicine Research Center, Iran

³Biochemistry, Bushehr University of Medical Sciences

⁴Cardiology, Bushehr University of Medical Sciences

Objectives: This study assessed the efficacy of oral consumption of N-acetyl cysteine (NAC) and melatonin (ML) in reducing early reperfusion injury and oxidative stress in patients with ischemic heart disease undergoing coronary artery bypass grafting (CABG) with respect to the measurements of, cardiac troponin T, tumor necrosis factor- α (TNF- α), lactate and malondealdehyde (MDA) levels in the blood.

Methods: This study was a randomized, open-label, placebo-controlled trial conducted with of 93 patients, aged between 39 to 76 and eligible for CABG, were recruited and randomly assigned into three intervention groups through a simple randomization method and underwent CABG surgery. Blood samples were withdrawn from arterial line, (1) before the induction of anesthesia, (2) before aortic cross-clamping, (3) during cross-clamp period, (4) 1 min and (5) 15 mints after declamping, (6) after recovery at the ICU. The blood samples were analyzed for TNF- α , lactate, troponin T and MDA levels by using ELISA Kits.

Results: There was no significant difference in influencing variables among the groups at the baseline. Overall mean TNF- α , lactate, and troponin T levels were significantly different between the intervention groups (all P0.001) at the recovery phase. Post-hoc pairwise comparisons showed that the differences of mean serum levels between ML and control groups were statistically significant for MDA, TNF- α , lactate, and troponin T (P0.001, P=0.001, P=0.001, respectively). The differences between NAC and control groups and between ML and NAC groups were only significant for mean lactate level (P0.001).

Conclusion: The current study revealed that ML and NAC are potent antioxidants with similar efficacy in terms of reducing CABG related cardiac injury and oxidative stress with the dosage employed for the intervention.

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Design a Clinical Program for Success

The Transition of Care for Pediatric Diabetes: From Hospital to Clinic Follow-up

Michael Yafi¹, Michelle Rivera Davila¹, Sem Ohland¹, Tong Han Chung², Sharif Mansur², Andrew Casas³

¹*Pediatric Endocrinology, UTHealth The University of Texas Health Science Center a Houston, USA*

²*UT Physicians Healthcare Transformation Initiatives, UTHealth The University of Texas Health Science Center a Houston, USA*

³*UTP Department: Management Information Office, Vice President, and Chief Operating Officer, USA*

Background: Monitoring the follow-up of newly diagnosed diabetes ketoacidosis (DKA) children is a cornerstone in pediatric diabetes care. Through the Texas Healthcare Transformation and Quality Improvement Program Medicaid 1115 Waiver, UT Physicians (UTP) and Memorial Hermann Hospital (MHH) has implemented an evidence-based transition of care program for diabetic children to ensure continuity of care from hospital discharge to clinic follow-up.

Objective: To evaluate the effectiveness of the transition of care program for DKA patients in the hospital.

Methods: This is a descriptive case study including DKA children who received transition of care services at MHH from October 2013 to September 2016.

Results: The 181 DKA patients at MHH were followed up in UTP outpatient clinic after hospital discharge. More than 90% of follow-up visits occurred within 3 months post discharge.

Conclusion: Establishing transition of care for DKA children ensures that patients receive the appropriate diabetes care from hospital to outpatient clinic. There are some cases in which parents have refused the diagnosis of diabetes, tried natural or religious therapies and failed to follow up for diabetes care for their children and many cases ended up with repeated DKA episodes or even death.

Our program has shown a remarkable results in which we were able to keep track of DKA children in transition of care from hospital DKA status to outpatient diabetes follow-up.

Design a Clinical Program for Success

Internet Based Training Techniques to Improve Therapeutic Results in Insulin Pump Users

Katerina Stechova¹, Miroslav Vanis^{1,2}, Pavlina Pithova¹, Milan Kvapil¹

¹Department of Internal Medicine, University Hospital Motol, Czech Republic

²Faculty of Transportation Sciences, Czech Technical University in Prague, Czech Republic

Background: By using modern devices (glucose sensors, insulin pumps) expected therapeutic targets are not always reached.

Objective: In WCTD 2016 we presented our observation that one important cause of these devices lower efficacy can be patient's eating behaviour. In current study, we are addressing the question how by using internet based training techniques in combination with classical education the situation can be improved.

Methods: In this study 26 DM1 patients, insulin pump users, were involved (13/14 F/M). Their further characteristics are (median, range): age 37 years (22-54), DM1 duration 13 years (1-32), HbA1c 68 mmol/mol (55-85) IFCC. At the beginning of this study the special re-educational session concentrated on diet was offered to them and they were encouraged to use regularly web based dietary application (NutriData) to check their diet. Moreover, special set of test questions (available on www.diabetickaasociace.cz) was prepared. Questions are focused on insulin pump therapy, glucose sensors as well as on general diabetes related topics with special attention to diet and insulin dose adjustment. From these questions, multiple choice type test (42 questions) can be generated on-line. Prior the test patients can try training version of the test how many times they want. To pass the test at least 80% correct answers are required. In the case of failure, patients can repeat this test, but with 2 weeks delay.

Results (median, range): overall test score was 86% (50-100%), 20/26 patients succeeded in the test, two of them in the second attempt. Questions on basic knowledge on diabetes were surprisingly most problematic. Higher test score correlated positively with lower HbA1c after 3 months ($p=0.027$).

Conclusion: Prior application of new treatment modalities patients can be trained and tested this way (resembling for example the driving licence receiving process).

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Next Generation of Diabetes Trials

Comparative Pharmacokinetics and Pharmacodynamics of a Proposed Biosimilar and Marketed Insulin Glargine in Patients with Type 1 Diabetes

Tim Heise¹, Ranitendranath Tagore², Charles Donnelly³, Abhijit Barve³, Anand Jacob²

¹*Diabetes, Obesity and Metabolism, Profil, Germany*

²*Biopharmaceuticals, Biocon Research Limited, India*

³*Diabetes, Mylan Inc, USA*

Background: MYL-1501D is a long-acting human insulin analogue with amino acid sequence, strength, and formulation identical to the reference product (insulin glargine), although both are manufactured by distinct processes.

Objective: This double-blind, randomized, 3-way crossover study compared the pharmacokinetics (PK)/pharmacodynamics (PD) of a proposed biosimilar insulin glargine (MYL-IG) with US- and EU-marketed insulin glargine (US-IG; EU-IG).

Methods: Patients with type 1 diabetes (T1D; N=114) received 0.4 U/kg of each insulin under automated euglycemic clamp conditions (Biostat, clamp level 100 mg/dL). Insulin glargine and metabolite M1/M2 concentrations ("INS"; measured by liquid chromatography–tandem mass spectrometry), and glucose infusion rates (GIR) were assessed over 30 hours.

Results: Insulin glargine M1 was found to be the primary moiety in circulation (as reported), with insulin glargine and M2 being undetectable. Bioequivalence between MYL-IG and both US-IG and EU-IG was demonstrated for the primary PK endpoints: area under INS curve ($AUC_{ins.0-30h}$) and maximum INS ($C_{ins\ max}$). Least squares mean ratios were close to 1, and 90% CIs were within 0.80 to 1.25 ($AUC_{ins.0-30h}$: 0.95-1.09 for MYL-IG/US-IG and 0.95-1.09 for MYL-IG/EU-IG; $C_{ins\ max}$: 0.99-1.12 for MYL-IG/US-IG and 0.97-1.10 for MYL-IG/EU-IG). The GIR profiles were nearly superimposable (Figure), and bioequivalence was also fulfilled for the primary PD endpoints ($AUC_{GIR0-30h}$: 95% CI, 0.80-1.10 for MYL-IG/US-IG and 0.82-1.14 for MYL-IG/EU-IG; GIR_{max} : 0.89-1.10 for MYL-IG/US-IG and 0.91-1.11 for MYL-IG/EU-IG). PK and PD equivalence was also demonstrated between US-IG and EU-IG, establishing a 3-way bridge between MYL-IG, US-IG, and EU-IG. All insulins were well tolerated. No injection site reactions occurred with MYL-IG.

Conclusion: In conclusion, PK and PD equivalence was shown between MYL-IG, US-IG, and EU-IG in patients with T1D.

Next Generation of Diabetes Trials

Comparable Immunogenicity between MYL-1501D and Insulin Glargine in Patients with Type 1 and 2 Diabetes Mellitus: Phase 3 INSTRIDE Studies

Bin Sun¹, Nilanjan Sengupta², Anita Rao², Nann Green³, Charles Donnelly¹, Abhijit Barve¹, Michael Ankersen¹

¹*Diabetes, Mylan Inc., USA*

²*Diabetes, Biocon Research Limited, India*

³*Diabetes, Eurofins Pharma Bioanalytics Services US Inc, USA*

Background: MYL-1501D is a long-acting human insulin analogue with amino acid sequence, strength, and formulation identical to the reference product (insulin glargine), although both are manufactured using different recombinant host cells and purified via distinct processes.

Objective: The aim of the INSTRIDE studies was to compare the safety and efficacy of MYL-1501D and insulin glargine in patients with type 1 and 2 diabetes mellitus (T1DM and T2DM).

Methods: Immunogenicity was assessed as a secondary endpoint using the safety population and included incidence and change from baseline in the relative levels of antidrug antibodies (ADA) and antibodies directed against host cell proteins (anti-HCP) as well as the comparison of ADA and clinical outcomes.

Results: In patients with T1DM, the results of the immunogenicity profiles were comparable between the MYL-1501D and insulin glargine treatment groups. The binding profiles for total ADAs were similar to insulin cross-reactive antibodies regarding actual and change from baseline values. The proportions of patients who tested positive for anti-HCP antibodies were similar between the treatment groups at all time points, with no statistically significant differences between them. Among patients with T2DM, the results of the immunogenicity profiles were comparable between the MYL-1501D and insulin glargine treatment groups. The incidence of total ADA and insulin cross-reactive antibodies were also comparable between the 2 treatment groups. The differences between the treatment groups in the proportion of patients who tested positive for anti-HCP antibodies were not statistically significant at any evaluable time points throughout the study.

Conclusion: In patients with T1DM and T2DM, immunogenicity profiles were comparable between MYL-1501D and insulin glargine treatment groups.

Next Generation of Diabetes Trials

Efficacy and Safety of MYL-1501D Compared with Insulin Glargine in Patients with Type 1 Diabetes:
The 52-week INSTRIDE 1 Study

Thomas C. Blevins¹, Abhijit Barve², Anand Jacob³, Bin Sun², Michael Ankersen²

¹*Diabetes and Endocrinology, Texas Diabetes and Endocrinology, USA*

²*Diabetes, Mylan Inc, USA*

³*Diabetes, Biocon Research Limited, India*

Background: MYL-1501D is a long-acting human insulin analogue with amino acid sequence, strength, and formulation identical to the reference product (insulin glargine), although both are manufactured by distinct processes.

Objective: The aim of the INSTRIDE 1 study was to compare the safety and efficacy of MYL-1501D with the reference product insulin glargine in patients with type 1 diabetes after 52 weeks of once-daily administration. The primary objective was to show noninferiority (0.4% margin) of MYL-1501D to insulin glargine when administered in combination with prandial insulin, as measured by change in HbA_{1c} after 24 weeks. The secondary endpoints were other metabolic readouts (eg, fasting plasma glucose, insulin dose, self-monitoring of blood glucose) as well as safety parameters (eg, adverse events, hypoglycemia, allergic reactions, immunogenicity).

Methods: After a 6-week run-in period on the reference product, patients (HbA_{1c} 10.5%) were randomized to receive once-daily MYL-1501D (n=280) or insulin glargine (n=278) in combination with thrice-daily mealtime insulin lispro for 52 weeks.

Results: MYL-1501D met the criteria for noninferiority to insulin glargine for change in HbA_{1c} from baseline to 24 weeks (95% CI [intent-to-treat population]: -0.066, 0.117). There were no significant treatment differences in other efficacy measures at 24 and 52 weeks. At week 52, there were similar findings in the 2 treatment groups for safety outcomes, including adverse events, hypoglycemia, allergic reactions, weight change, and antidrug antibodies.

Conclusion: Both MYL-1501D and insulin glargine, when used in combination with prandial insulin, were effective and had similar metabolic and safety profiles.

Next Generation of Diabetes Trials

Efficacy and Safety of MYL-1501D Compared with Insulin Glargine in Patients with Type 2 Diabetes: The 24-week INSTRIDE 2 Study

Michael Ankersen¹, Thomas C. Blevins², Anand Jacob³, Abhijit Barve¹, Bin Sun¹

¹*Diabetes, Mylan Inc, USA*

²*Diabetes and Endocrinology, Texas Diabetes and Endocrinology, USA*

³*Diabetes, Biocon Research Limited, India*

Background: MYL-1501D is a long-acting human insulin analogue with amino acid sequence, strength, and formulation identical to the reference product (insulin glargine), although both are manufactured by distinct processes.

Objective: The aim of the INSTRIDE 2 study was to compare the safety and efficacy of MYL-1501D with the reference product insulin glargine in patients with type 2 diabetes (T2D) after 24 weeks of once-daily administration. The primary objective was to show noninferiority (0.4% margin) of MYL-1501D compared with insulin glargine when administered once daily in combination with oral antidiabetic drugs (OADs), as measured by change in HbA_{1c} after 24 weeks. The secondary endpoints were other metabolic readouts (eg, fasting plasma glucose, insulin dose, self-monitoring of blood glucose) as well as safety parameters (eg, adverse events, hypoglycemia, allergic reactions, immunogenicity).

Methods: The study enrolled 560 patients with T2D who were either insulin-naïve (HbA_{1c} 9.5%, n=230) or had been on stable once-daily insulin glargine for at least 3 months before randomization and 2 or more OADs. Patients were randomized to once-daily MYL-1501D (n=277) or insulin glargine (n=283) for 24 weeks and continued their OADs.

Results: MYL-1501D met the criteria for noninferiority to insulin glargine for change in HbA_{1c} from baseline to 24 weeks (95% CI [intent-to-treat]: -0.098, 0.218). There were no significant treatment differences in other efficacy measures at 24 weeks. There were similar findings in the 2 treatment groups for safety outcomes, including adverse events, hypoglycemia, allergic reactions, weight change, and antidrug antibodies. Similar efficacy and safety profiles were also observed between the 2 treatment groups within the insulin-naïve and insulin-treated subgroups.

Conclusion: Both MYL-1501D and insulin glargine, when used in combination with OADs, were effective and had similar metabolic and safety profiles.

Next Generation of Diabetes Trials

Zygosids - the Novel Family of Complexes for Treatment and Prevention of Type 2 Diabetes

Mordechai (Mottie) Chevion^{1,2}, Vladimir Vinokur¹, **Dror Chevion**²

¹*Department of Biochemistry and Molecular Biology, The Hebrew University of Jerusalem, Israel*

²*Management, Concenter BioPharma (Silkim Ltd.), Israel*

Background: Components of the immune system are altered in obesity and type 2 diabetes (T2D), with the most apparent changes occurring in adipose tissue, the liver, pancreatic islets, and the circulating leukocytes. Inflammation is a major player in T2D. Also, a causal role, in T2D, was suggested and demonstrated for the accumulation of iron within the beta-islets and peripheral adipose tissues.

Objectives: To examine the anti-T2D therapeutic efficacy of Zygosids - novel safe drugs, with anti-inflammatory properties and iron chelation capacities.

Methods: The *Psammomys obesus* (sand rat) model of diet-induced T2D was used. The animals were fed high energy diet (HED) and became diabetic by Day 25 (blood glucose level (BGL) 300 mg/dl). Treatment of these diabetic animals with a Zygosid (by i.p. injections of 2 or 6 mg/kg/treatment, 3-times/week) was started on Day 27 and continued until Day 63. In an additional set of experiments, the prophylactic treatment was started on Day 1 together with the animals' transferring to HED. Body weight and BGL was monitored throughout the study in both sets of experiments. Additional tests were conducted at the end of the study.

Results: Treatment of the diabetic animals for 12-15 days caused a complete reversal and downturn of BGL to its normal range (100 mg/dl). The treatment also restored normal body weight as well as serum insulin, ALT, LDL, and triglycerides levels, and reduced the histology score associated with NAFLD. Additionally, the treatment caused a marked reduction in insulin resistance of the diabetic animals as evidenced by a follow-on GTT trial.

Similarly, prophylactic administration of a Zygosid yielded 50% inhibition in the elevation of BGL during the experiment and ameliorated hyperinsulinemia.

Conclusion: Zygosids demonstrated an exceptionally high therapeutic efficacy in both prevention and treatment of T2D. Importantly, no adverse effects were detected.

Next Generation of Diabetes Trials

Pregnancy Outcomes: Effects of Metformin (POEM) Study in Gestational Diabetes Mellitus

A Long Term Randomized Controlled Trial

Adriaan Kooy

Investigator Initiated Research, Bethesda Diabetes Research Center, Netherlands

Internal Medicine, University Medical Center Groningen, Netherlands

Internal Medicine & Diabetology, Treant Care Group, Netherlands

Background: Gestational Diabetes Mellitus (GDM) is a precursor of type 2 diabetes (T2D). Insulin resistance is an important causal factor in GDM and T2D. Insulin added to diet as the standard care for GDM has disadvantages: extra weight gain, increase of blood pressure, and risk of hypoglycaemia. We do not prevent these disease mechanisms by enhancing hyperinsulinaemia, but potentially by lowering insulin resistance. Metformin may do so.

Objective: To study the effects of metformin in GDM on health outcomes in mother and child.

Methods. 500 pregnant women with GDM (week 16-32) will be included and randomized (1:1) to either *metformin on top of standard care (850 mg up to thrice daily)* or *standard care alone*. Insulin rescues will follow in both arms if needed. GDM: fasting plasma glucose ≥ 5.3 mmol/l and/or plasma glucose ≥ 7.8 mmol/l two hours after 75 gram glucose orally. Three phases: A (inclusion until 2 weeks after delivery); B (2-52 weeks after delivery); C (1-20 years after delivery). The intervention starts at the diagnosis GDM and continues in phase A and B. Breastfeeding will be encouraged. Phase C is observational. Each mother may *re-entry* phase A after another pregnancy in phase B or C. 800-1000 pregnancies and children will be studied. POEM study has been sufficiently powered (N=500) based on the primary aggregated endpoint of eight important clinical endpoints: (1) pregnancy related hypertension, (2) large for gestational age baby, (3) premature delivery with a gestational age ≤ 37 weeks, (4) instrumental delivery, (5) caesarean delivery, (6) birth trauma, (7) neonatal hypoglycaemia, (8) neonatal intensive care.

Results. We hypothesize that metformin early given during GDM will improve important clinical outcomes.

Conclusion. The POEM study may help to improve international guidelines for the treatment of GDM. The community in clinical diabetes asks for such an RCT.

Pragmatic Trials

Hypomagnesaemia in Diabetes Patients: Comparison of Serum to Intracellular Measurement of Responses to Magnesium Supplementation and its role in Inflammation

Nadia Zghoul¹, Nada Alamaldin¹, IvanTong Mak², Adel Ahmed¹, Narayanam Nampoory(†)¹, Burton Silver³, William Weglicki²

¹Clinical Research Unit, Dasman Diabetes Institute, Kuwait

²Department of Biochemistry and Molecular Medicine, George Washington University, USA

³IntraCellular Diagnostics, Inc, USA

Background: Magnesium supplementation in diabetes patients with hypomagnesaemia was shown to diminish inflammatory parameters including CRP, TNF α , and oxidative stress parameters. However, serum magnesium levels only represent less than 1% of total magnesium; whereas cellular Mg deficiency is a more reliable parameter for assessing Magnesium. In most diabetes patients where hypomagnesaemia occurs the important depletion of cellular levels is usually not measured.

Objectives: In this clinical trial we assessed the efficacy of oral magnesium supplementation in Type 2 diabetes Patients in restoring serum (extracellular) and mucosal cell (intracellular) Mg levels. The study has two co-primary endpoints, the change in serum and intracellular magnesium level between baseline and after three month supplementation. Additionally, we compared the efficacy with regard to lowering HbA1C, CRP, TNF α and Isprostane as secondary endpoints.

Methods: In an open label trial, 47 hypomagnesaemic type 2 diabetes patients were enrolled and administered 2x providing 336mg Magnesium. The study was registered under <https://clinicaltrials.gov/ct2/show/NCT01980459>. At baseline and after three months, serum, cellular Magnesium and inflammation biomarkers were measured. For Intracellular Magnesium levels, sublingual epithelial cells were obtained noninvasively from each patient and fixed on slides prior to assay by analytical SEM using computerized elemental X-ray analysis. Blood samples were analyzed monthly for Magnesium levels, Creatinine, HbA1C and CRP. Systemic inflammatory markers including Substance P, Tumor Necrosis Factor alpha and oxidative stress marker Isprostane were also determined using sandwich ELISAs before and after treatment.

Results: The repletion of serum and cellular Mg will be correlated with inflammatory, oxidative stress and diabetes markers before and after treatment to assess which parameter correlates best with efficacy in lowering inflammation.

Conclusion: Our results may support a wider application of the cellular magnesium assay with other diseases than diabetes where magnesium and glucose homeostasis are impaired.

Pragmatic Trials

Assessing Health Literacy: A Potential Useful Indicator in Diabetes Clinical Trials

Xavier Debussche^{1,2}, Maryvette Balcou-Debussche³

¹CIC 1410 INSERM, CHU Réunion, Reunion

²Endocrinology, CHU Felix Guyon, Reunion

³ICARE Research Unit, University of Reunion Island - ESPE, Reunion

Background: Health literacy (HL) refers to the social and cognitive skills for accessing, understanding and using health informations and services to maintain health. It is a multidimensional concept, not limited in its modern acception to the sole ability in reading and interpreting health information or medical recommendations. HL is a known determinant of health outcomes but has been seldom used in clinical trials, either for the description of enrolled participants, or as an outcome.

Objective: To assess HL of participants in the ERMIES RCT, designed to compare self-management education (SME) maintained over 2 years to a short, 3 month long, SME course.

Methods: The ERMIES study enrolled 101 patients with type 2 diabetes (T2D), HbA1c \geq 8%. Health literacy was explored via the Health Literacy Questionnaire (HLQ, 44 items, 9 independent scales). It was completed by 66 participants. HL profiles were analyzed via descriptive statistics and compared to a control population of 119 T2D outpatients.

Results: Important issues were observed in appraisal of health information (HLQ, scale 5), ability to find good health information (scale 8), and understanding health information well enough to know what to do (scale 9). The better HL strengths of participants were found for feeling understood and supported by healthcare providers (scale 1), ability to actively engage with healthcare providers (scale 6), and navigating the healthcare system (scale 7). Scale 7 showed the highest score (CI95% [3-,33-3,67]) compared to controls (CI95% [3-,60-3,84], p=0,064).

Conclusion: In this exploratory pilot study, participants of the ERMIES study showed a high mean score in some HL scales, especially « Navigating the health care system ». HL could be a useful tool in clinical trials to describe populations, detect potential selection bias, and situate enrolled participants in the relation to health and resources for health.

Pragmatic Trials

Improvement of Type 2 Diabetes (T2DM) in 250 Hypogonadal Men with Testosterone Therapy for 8 Years: Real-life Registry Data

Farid Saad^{1,4}, Karim Haider², Gheorghe Doros³, Ahmad Haider²

¹Medical Affairs Andrology, Bayer AG, Germany

²Urology, Private Urology Office, Germany

³Epidemiology and Statistics, Boston University School of Public Health, USA

⁴Research, Gulf Medical University, United Arab Emirates

Background: Up to 50% of men with T2DM are hypogonadal.

Objective: Registry to study effectiveness and safety of testosterone undecanoate injections (TU).

Methods: In a urology office, 133 men received TU 1000 mg/12 weeks (T-group), 117 had opted against testosterone therapy (TTh) and served as controls (CTRL). Measurements were performed 1-4 times/year for up to 11 years. 8-year data are reported. Mean changes over time between groups were compared by mixed effects model for repeated measures with random effect for intercept and fixed effects for time, group and their interaction and adjusted for age, weight, waist circumference, fasting glucose, blood pressure and lipids to account for baseline differences between groups.

Results: 250 of 696 hypogonadal men (36%) had T2DM, diagnosed and treated by their family physician.

Age (years): 61.8±5.4 (T-group), 64.9±4.3 (CTRL).

Mean HbA_{1c} progressively decreased from 8.8±0.9 to 6.1±0.4% after 8 years in the T-group (p0.0001). In CTRL, HbA_{1c} increased from 7.5±0.5 to 8.2±0.5% (p0.0001), estimated adjusted difference between groups: -3.1% (p0.0001).

Fasting glucose decreased from 7.6±1.1 to 5.3±0.1 mmol/L (p0.0001) in the T-group and slightly increased from 5.8±0.3 to 5.9±0.3 mmol/L in CTRL (NS), estimated adjusted difference between groups: -0.8 mmol/L (p0.0001).

HOMA-IR (only available for the T-group) decreased from 10.2±2.0 to 3.6±0.8 after 8 years (p0.0001).

Insulin (only available for the T-group) decreased from 29.6±4.2 to 15±3.4 mU/L (p0.0001).

At baseline 54 patients in the T-group were on insulin and received a mean dose of 32.4±12.1 units. The mean dose requirement declined to 19.7±11.0 (p0.0001).

In the T-group, 106 (80%) achieved HbA_{1c} 6.5%. In CTRL, only 1 patient achieved HbA_{1c} 6.5%.

Conclusion: Long-term TTh with TU in hypogonadal men with T2DM improved glycaemic control compared to untreated controls. Correcting hypogonadism in men with T2DM supports standard diabetes treatment.

Pragmatic Trials

A Phase 2a Trial of DMX-200: Synergistic Blockade of AT1R and CCR2 in a Subgroup of Patients with Diabetic Nephropathy

David Packham¹, Matthew Roberts², Stephen Holt³, Williams James⁴, Harrison Kathryn⁴, David Power⁵

¹Nephrology, Melbourne Renal Research Group, Australia

²Nephrology, Eastern Health, Australia

³Nephrology, Royal Melbourne Hospital, Australia

⁴Board and Management, Dimerix Bioscience, Australia

⁵Nephrology, Austin Health, Australia

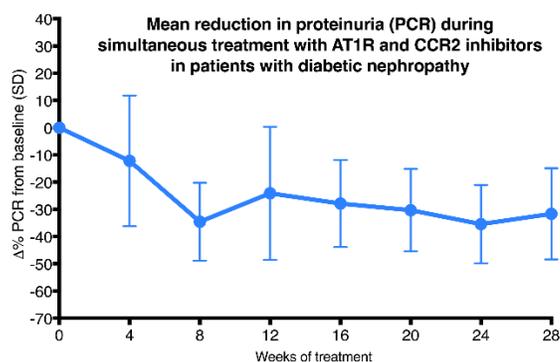
Background: The angiotensin II receptor type 1 (AT1R) and chemokine receptor 2 (CCR2) are G protein-coupled receptors that form functional heteromers. Simultaneous antagonism of these receptors has a beneficial effect on proteinuria in the sub-total nephrectomy rat model of nephrotic syndrome, and we predict this effect may be beneficial for patients with Diabetic Nephropathy (DN) where residual proteinuria is likely a surrogate biomarker of clinical benefit.

Objective: To explore the effect of simultaneous administration of the AT1R-inhibitor irbesartan and the CCR2-inhibitor propagermanium on proteinuria in patients with DN.

Methods: Patients (n=27) with a range of proteinuric diseases were enrolled in an open label, Phase 2a, dose escalation study (DMX-200-201) in Australia to determine the safety of 30-240 mg daily dose of propagermanium. Patients received stable irbesartan for ≥ 3 -months prior to enrolment and throughout the study. An informal subgroup analysis was conducted on biomarkers of proteinuria in patients with DN on 150-300 mg irbesartan (analysis population).

Results: The average age of DN patients was 65 ± 10 (SD) years. The baseline eGFR was 28 ± 14 (range 17-59) ml/min, PCR 265 ± 205 mg/mmol (range 70-700). There were no clinically relevant changes to safety parameters. Of the 9 patients in the analysis population, 5 (55%) had a 50% reduction of proteinuria from baseline during the study, and there was a mean reduction in PCR of 31.9% after 28-weeks of treatment. To confirm this trend, data was analyzed using a repeat-measures, mixed model of proteinuria values throughout the study. This test suggests that DN patients showed significant reduction from baseline values for PCR and 24-hour protein excretion.

Conclusion: These data support the future conduct of randomised controlled trial to determine the beneficial effects of the CCR2 receptor antagonist propagermanium in addition to established AT1R blockade in patients with DN.



Precision Medicine in Diabetes

Metabolic Syndrome, Multisystem Disease

Dragan Klaric

Nephrology and Dialysis, Zadar General Hospital, Croatia

Background: Obesity, hyperglycemia, dyslipidemia and hypertension, as well as many other disorders such as non-alcoholic fatty liver disease (NAFLD) are known to be part of metabolic syndrome (MS). Pathophysiological mechanisms are clear, but the dilemma remains in the cause of this multisystemic disorder of high cardiovascular risk.

Objective: We present a 35-year-old man with MS and NAFLD and a series of `randomly detected` disorders: hypothyroidism, hyperparathyroidism, diabetes mellitus, sleep apnea, and colon polyps. The patient presented to our institution with nephrocolics and spontaneous evacuation of kidney stones. Status: BW, 120kg; BH, 185cm; waist circumference, 113cm; BMI 34.5; BP, 175/90mmHg.

Methods of examination: Abdominal ultrasound: On the right kidney is a smaller concrement. Fundus hypertonicus grade I. ABP, 24h average 148/99 mmHg, non-dipper. Polysomnography: obstructive sleep apnea. AHI, 34.9. Liver biopsy: Chronic steatohepatitis on the verge of cirrhosis. Fibroscan: median stiffness, 25.4 Kpa; IQR, 5.7 Kpa; IQR, med 22%. Thyroid sonography: diffuse disease, struma. Gastroscopy: Barrett`s esophagitis. Colonoscopy: Polyp in the caecum.

Results of laboratory: Glucose, 7.7 mmol/L; ALT, 134 U/L; AST, 74 U/L; S-ALP, 101 U/L; GGT, 127 U/L; HbA1C, 9.0%; AFP, 2.1 U/mL; PTH, 13.29 pmol/L; cholesterol, 5.1 mol/L; HDL, 0.74 mol/L; LDL, 3.581 mol/L; Vitamin D3 (25-OH), 32 mol/L; aldosterone, 622 pmol/L; renin activity, 0.9 mcg/L/hour; K, 3.1 mol/L; Ca, 2.28 mol/L; P, 0.82 mol/L; CRP, 6.8 mg/L; TSH, 5.19 mIU/L; CrC, 151.1 ml/min; proteinuria, 0.26 g/24h; Ca (urine), 17.32 mmol/24h (2.50 to 7.50); P (urine), 54 mmol/24h.

Conclusion: The patient presented with nephrocolic accompanied with hypercalciuria, indicating hyperparathyroidism. The patient`s obesity is dominant in the clinical presentation, along with components of MS and NAFLD. The question is whether the NAFLD is a component of MS or it is a systemic disease with dominant non-alcoholic liver disease and multi-organ damage. Endocrinopathy and colon polyps are also present in this case.

Precision Medicine in Diabetes

Glycemic Control Trajectories Prior to Initiation of Injectable Treatment among Adults with Type-2 Diabetes: A Real-world Observational Study

Orna Reges, Becca Feldman, Tomas Karpati, Morton Leibowitz, Ilan Gofer, Ran Balicer, Maya Leventer-Roberts
Clalit Research Institute, Clalit Healthcare Services, Israel

Background: Injectable therapy is often initiated when a patient with type-2 diabetes does not achieve glycemic control. However, the timing of when injectable therapy is initiated may be delayed. Identification of patterns of deterioration in HgbA1c concentration in the pre-injection period may improve understanding of characteristics of individuals with oral therapy failures and highlight risk strata to inform future clinical outcome prediction studies.

Objective: To identify clusters of HbA1c concentration trajectories over the 5 years previous to the initiation of injectable therapy.

Methods: A cohort of 36,273 adults with at least 5 years duration of type-2 diabetes, who initiated injectable therapy anytime during 2010-2014 (index-date), were identified in Israeli electronic medical records. HbA1C means (SD) were calculated for each of the five years prior to the index-date. Latent class analysis was used to identify clusters of patients with similar HbA1c-trajectories.

Results: Four clusters were identified: 1) Included 29,432 patients with a mean (SD) HbA1c of 7.3% (1.1%) 5 years prior to the index-date (referred to as 5-year mean), that increased to 8.9% (1.6%) at index-date; 2) Included 3,565 patients with a 5-year mean (SD) of 9.4% (2.6%), which gradually increased to 11.3% (1.5%) after 3 years and remained stable up to index-date; 3) Included 1,803 patients with a 5-year mean (SD) of 11.5% (1.2%), which improved to a mean of 8.6% (1.5%) at 2 years before index-date but reverted to 10.5% (2.0) at index-date; and 4) Included 1,365 patients with a stable mean HbA1c (7.5%), which steeply increased after 3 years up to 13.6% (1.5) at the time of index-date.

Conclusions: Injectable therapy was mostly initiated following a gradual deterioration in glycemic control. For some patients, therapy was initiated when the patient had severe hyperglycemia preceded by different patterns of HbA1c trajectories. The association between these trajectories and future outcomes need be investigated in future research.

Regulatory Trends in Diabetes

Energetic Balance: Feedback for Insulin Delivery Monitoring Applied to Hyperglycemic Non-Diabetic Type One Patients

Novikov V K^{1,2}, Devriendt J³, **Sebastian DOBOS**⁴, Coulic V^{2,3}

¹*Intensive care & Transplantation, VN Sklifosovski Emergency Scientific Research Institute, Russia*

²*Laboratory of Translational Medicine, Free Brussels University, Belgium*

³*Intensive Care Unit, CHU Brugmann, Belgium*

⁴*Digestive Surgery, CHU Brugmann, Belgium*

Background: At WCTD-2016, differential temperature evolution as feedback for insulin delivery monitoring (ADD-CIT) was shown useful in the treatment of glucose metabolism life threatening alterations in DM1 patients.

Objective: to verify our basis hypothesis applying ADD-CIT treatment to other acute glucose metabolism disorders.

Methods: Groups considered for ADD-CIT sessions included: DM2 patients (18), patients with severe heart pathology without known diabetes (27) or with DM-2 (18), DM-1 patients (14) for comparison.

Control group receiving usual insulin treatment with exclusive glycaemia monitoring included: DM-2 patients (9), heart pathology (post-surgery – 15) and ARCA patients (24). 11 healthy volunteers were investigated. Initial glycaemia 11.1mm/l was the main inclusion criterion (after informed consent) for all 125 patients. Age, sex, BMI were comparable, observation extended up 8 hours. Besides usual clinical investigations glycaemia was controlled every hour by strip (Accutrends, USA) or gasometer analysis (ADL-90-Flex).

Results: In the different ADD-CIT groups a glycaemia decrease of 30-40% of the initial value was noted within 2-4 hours with further stabilization at levels 11.1mm/l. In controls this result was attained after 4-7 hours with frequent yo-yo phenomena. No correlation was observed between Dt values and glycaemia levels. Dt values were negative only in decompensated DM-1, decreased during ADD-CIT treatment of DM-2, increased at the end of any successful session, trending towards the mean values observed in healthy control. If Dt accused an abnormal fall, cautious glucose injection corrected the situation without glycaemia alteration.

Conclusion: In spite of the small, not quite correctly matched series, differences in tempi and importance of glycaemia fall between the groups treated with Dt monitoring and control groups confirm the usefulness of this approach, independently on the pathology leading to acute hyperglycemia. Further studies will be conducted to examine the possibility of “energetic feedback” application to chronic hyperglycemia management.

Regulatory Trends in Diabetes

Gene Polymorphisms of Tumor Necrosis Factor Alpha and Plasma Vitamin D in Children with Type I Diabetes Mellitus

Tatjana Jevtovic Stoimenov, Dusica Pavlovic, Tatjana Cvetkovic, Ivana Stojanovic, Jelena Basic, Milena Despotovic
Department for biochemistry, University of Nis, Medical faculty, Serbia

Background: Gene polymorphisms in the regulatory regions of TNF-alpha and metabolism of vitamin D may play a contributory role in the pathogenesis of type I Diabetes Mellitus (T1DM).

Objective: Thus, the aim of this study was to examine the association of TNF-alpha G-308A polymorphisms and level of plasma 25-OH D3 in children with T1DM

Methods: A total of 138 patients with DMI and 123 healthy controls were screened for TNF-alpha G-308A polymorphisms using the polymerase chain reaction-restriction fragment length polymorphism method. Liquid chromatography tandem mass spectroscopy (LC-MS) was applied for the direct measurement of 25(OH)D in human plasma.

Results: The genotype and allele frequencies distribution of TNF-alpha G-308A gene polymorphisms did not show differences between patients and controls ($p=0.166$). But level of 25(OH)D3 is significantly reduced in patients compared to healthy control. The lowest 25(OH)D3 level was found in the group of patients with TNF alpha A genotype compared to GG genotype patients ($p=0.05$).

Conclusions: In conclusion, our results showed that 25(OH)D3 level was significantly lower in T1DM patients, TNF alpha -308 G/A polymorphism is not associated with T1DM patients, and also for the first time we suggest an association of TNF alpha -308 AA genotype with lower level of 25(OH)D3 in children with T1DM in Serbian population.

Regulatory Trends in Diabetes

Association of Transforming Growth Factor BETA-1 (TGFB 1) and Type 1 Diabetes in Algerian Population

Rachida Raache¹, Esmâ Mihoubi¹, Habiba Amroun², Siham Belarbi¹, Nawel Benhalilou¹, Chafia Touil-Boukoffa¹, Nabila Attal²

¹Biology, Laboratory of Cellular and Molecular Biology (LBCM), Cytokines and NO Synthases, University of Bab-Ezzouar (USTHB), Algeria

²Immunology, Immunology Department, Pasteur Institute of Algeria (IPA), Algeria

Background: Type 1 diabetes (T1D) is a multifactorial autoimmune disease with complex genetic inheritance where cytokines play prominent roles.

Objective: To identify additional genetic markers, we tested polymorphisms in regulatory regions of TGF beta1 gene in our population. These polymorphism exhibit functional consequences for expression and function.

Methods: TGF-beta(1) single nucleotide polymorphisms at positions +869 (C or T, codon 10) were examined in 70 T1D patients and 74 healthy controls using Polymerase Chain Reaction Sequence Specific Primers (PCR- SSP). Results: Our results show significantly increased C allele frequency in patients when compared with control (71.4% vs 43.24%, P 0.01). Genotype analysis shows that TT genotype is more frequent in T1D than control (p= 0.03) the ORs (95% CI) were 2.11 (2.01- 5.35). Whereas decreased T1D risk association was obtained with TC genotype [OR: 0.53 (CI = 0.30- 0.94)].

Conclusions: Our preliminary results suggested that the TGF-β1 +869C/T polymorphism may be involved in Algerian type 1 diabetes susceptibility.

Regulatory Trends in Diabetes

Deficiency of Vitamin D in Type 1 Diabetes in Algerian Population

Raache Rachida¹, Ema Mihoubi¹, Melha Azzouz³, Nesrine Zabat², Abdelghani Aissou², Aissa Boudiba³, Chafia Touil-Boukoffa¹, Nabila Attal²

¹*biology, Laboratoire des cytokines et NO Synthases (FSB-USTHB), Alger, Université des Sciences et de la Technologie Houari Boumediene (USTHB), Alger, Algérie,, Algeria*

²*Immunology, département d'Immunologie, Institut Pasteur D'Algérie (IPA),, Algeria*

³*Diabetology, Service de diabétologie CHU Mustapha, Alger, Algérie,, Algeria*

Background: Epidemiological data have established a link between vitamin D deficiency and an increased incidence of T1D, whereas early and long-term vitamin D supplementation may decrease the risk of these disorders.

Objective: to examine the association of VD susceptibility to T1DM in the Algerian population
Methods: we studied 31 individuals with type 1 diabetes diagnosed according to the World Health Organization criteria and 57 control subjects. VD dosage was performed using Chimulinescence. Data were analysed using the x 2-test.

Results: a significantly higher frequency of vit D, HbA1c, peptide C was found in T1D vs. Controls Vit D :(8.19±5,19 vs. 10.04±5.02 ng/ml, p 0,005), HbA1c :(11.51±3,24 vs. 6 ±12 %, p 0.005).

Conclusion: Our results indicate that VD is associated with increased risk of T1DM in Algerian population.

Tech Companies in Clinical Research

Screening of Abuse Drugs and Clinical Laboratory Tests in Whole Blood and Urine Samples of Abusers

Majid Rezaei Basiri^{1,2}, Mahmoud Ghazi-Khansari^{1,3}, Mojgan Behshid⁴, Saleh Alilou⁵, Haniyeh Mohebbi-Kamali⁵, Marziyeh Mokhtari⁵, Fatemeh Hosseindoust⁵, valiyollah Watani⁵, Ladan Aminzadeh⁵, Fatemeh Seyed Nejad⁵, Ashraf Razavi⁵

¹*Welfare organization, Welfare organization of East Azarbayjan, Tabriz / Iran., Iran*

²*Department of pharmacology and toxicology, Department of pharmacology and toxicology, School of Pharmacy, Tabriz University of medical sciences, Tabriz / Iran., Iran*

³*Department of pharmacology and toxicology, Department of pharmacology and toxicology, School of Medicine, Tehran University of medical sciences, Tehran / Iran., Iran*

⁴*Nursing and midwifery, School of Nursing and midwifery, Tabriz University of medical sciences, Tabriz / Iran., Iran*

⁵*Welfare organization, Welfare organization of East Azarbayjan, Tabriz / Iran., Iran*

500 urine and 500 the whole blood samples of abusers were examined for the presence of alkaloid substances and abuse drugs in urine and blood. The all of samples were tested through as a view of clinical laboratory methods. In this study all abusers were male and female and their ages were (Mean±SD = 45±15)and they filled questionnaire and satisfy forms too. First all Fresh urine and blood samples were examined to confirm presence morphine, codeine, heroin, methadone, Tramadol, cannabis, Amphetamine, presence methamphetamine, Buprenorphine... depend on their addiction, so all samples were confirmed by two tests. Then they were examined to other clinical laboratory tests. All data analyzed with one way and two way Anova Turkey and Pvalue of this study for some study groups were P =0.0001.

The results of this study were showed that 4% of abusers had mild increase in hematocrite level and 2% of narcotic drugs abusers had mild lower level of blood sugars than normal range and 4% of participants had increase liver enzymes: ALT, AST, ALP and 1% of them had renal failure. Although blood level BUN and creatinin were examined to evaluation of their renal failure .The results in Tabriz/Iran undrevision of welfare organization clinics were approximately showed that all of study populations had positive results of addiction in each of urine and blood samples. Because some of abusers directly consumed full long time agonist or partial agonists drugs such as methadone and Buprenorphine for their maintance therapy in clinics. We conclude that between all drug analytical methods the cheapest and easiest tests of opioids and drugs in urine and blood samples is strip test for rapid diagnosis and thin-layer chromatography (TLC) is appropriate confirmation method to drug abuse distinguishing. Also doing test on blood samples have high importance in distinguishing and confirmation of drugs abuse in samples.

Translational and Preclinical Trends in Diabetes

Pharmacological Inhibition of Adipose Triglyceride Lipase (ATGL) Corrects High-Fat Diet-Induced Insulin Resistance and Hepatosteatosis in Mice

Gernot Grabner, Robert Zimmermann

Institute of Molecular Biosciences, University of Graz, Austria

Background: High plasma fatty acid (FA) concentrations are a well-established risk factor for the development of insulin resistance, type-2 diabetes, and non-alcoholic fatty liver disease (NAFLD). Although the mechanistic basis of this association is not entirely clear, inhibition of FA mobilization in white adipose tissue (WAT) represents a rational approach to lower plasma FA concentrations and to prevent the development of the aforementioned metabolic disorders.

Objective: The mobilization of fatty acids (FAs) from fat depots strongly depends on adipose triglyceride lipase (ATGL). Studies in ATGL-knockout animals revealed that these mice exhibit reduced plasma FA levels, increased insulin sensitivity and do not develop high-fat diet-induced insulin resistance. Here we investigated whether pharmacological inhibition of ATGL can improve the metabolic phenotype of obese, insulin-resistant mouse models.

Methods: Mice set on a high-fat diet were treated with the ATGL inhibitor ATGLISTATIN which was mixed in the diet.

Results: Atglistatin treatment caused a transient inhibition of lipolysis in the postprandial phase. This was associated with reduced plasma lipid, glucose, and insulin level. Importantly, Atglistatin prevented and reversed NAFLD and glucose intolerance. These beneficial effects of Atglistatin were observed in wildtype mice receiving high-fat diet and in a genetic model of obesity (ob/ob mice).

Conclusion: Our study provides profound evidence that transient inhibition of ATGL-driven lipolysis by the selective inhibitor Atglistatin corrects glucose intolerance and fatty liver steatosis. Pharmacological inhibition of ATGL activity in humans may represent a useful strategy to combat co-morbidities of obesity.

Translational and Preclinical Trends in Diabetes

Offspring of Parents with Obesity
Complex Investigations

Renata Wasik¹, Maria Dziura², Aleksander Basiak¹

¹*Department of Endocrinology for Children and Adolescents, Medical University Wroclaw, Poland*

²*Internal Medicine, Medical Center in Lubin, Poland*

Aim of the study: to examine offspring of patients with simple obesity. To ascertain, if there are some disturbances in the carbohydrate or lipid metabolism or unknown type 2 diabetes in these subjects.

Method and subjects: examined were 132 families, 108 families with obesity, and 24 families without obesity, the control group. 14 additional were excluded because of ascertained at the time of examination unknown type 2 diabetes in the parents. In all of the offspring and their parents performed were: weight, height, BMI, WHR HDL, TGD, LDL, glycaemia HbA1c, in the offspring additional HOMA. The control group included 30 healthy subjects with a negative anamnesis of obesity and/or diabetes in the family.

Results: Observed was overweight and obesity in a high percentage, increased BMI, WHR, significant differences in the level of HDL, TGD, LDL and HOMA between the examined and control group. Additional introduced was HHR

Translational and Preclinical Trends in Diabetes

Endogenous Molecules as Candidate Early Indicator for Type-2 Diabetes

Christina Yap, Anuar Zaini, Arun Mahendran

Jeffery Cheah School of Medicine and Health Sciences, Monash University Malaysia, Malaysia

Background: Type 2 diabetes is a metabolic disorder and early diagnosis is crucial for preventing onset of diabetes and its complications. Endogenous molecules reflects the fate of metabolic processes. CYP2E1, a member of the cytochrome P450 superfamily plays important roles in metabolism of many endogenous and exogenous compounds. Recent studies have shown that CYP2E1 expression in peripheral lymphocytes is elevated in diabetes and nephropathy hence, could be a candidate early indicator for diabetes risk.

Objective: The aim of this research was to 1) Optimize and validate a targeted approach for quantitating CYP2E1, 2) Assess the applicability of CYP2E1 quantitation alongside clinical indices currently used for diagnosis of type 2 diabetes (HbA1c and fasting blood glucose (FBG)) and 3) Assess the correlation of circulating CYP2E1 protein amounts with CYP2E1 gene expression and reactive oxygen species levels (ROS).

Method: Fasting blood samples were collected from healthy (control; C), pre-diabetes (PD) and diabetic (D) individuals. HbA1c, ROS and FBG were quantitated from plasma. Lymphocytes were isolated for gene expression analysis and preparation of unique CYP2E1 peptides. CYP2E1 was quantitated using QQQ-LCMS.

Results: Findings of this study showed the means of CYP2E1 amounts for PD and D groups were significantly higher than the C group ($p < 0.001$). No significant difference was seen between the means of PD and D groups ($p = 0.905$). CYP2E1 gene expression showed up regulation even when HbA1c was still within normal reference limits.

Conclusion: Observations from our study suggested CYP2E1 is an earlier indicator for diabetes in comparison to HbA1c and FBG.

Other

Benefits of Three Physical Therapy Modalities on Dermal Blood Flow in Type 2 Diabetic Patients with Peripheral Disease in Leriche-Fontaine Stage I

Guillermo A. Matarán-Peñarrocha

Distrito Sanitario Málaga. Servicio Andaluz de Salud. Málaga. España

Background: Type 2 diabetes is one of the main causes of peripheral vascular disease. Peripheral arterial disease is an indicator of widespread atherosclerosis, and an important marker of cardiovascular risk. The beneficial effects of exercise on glucose homeostasis include a marked stimulation of blood glucose utilization during and after its performance.

Objective: The objective of this study was to determine the effects of a program of 3 physical therapy modalities on feet dermal blood circulation in patients with type 2 diabetes with peripheral arterial disease.

Method: A randomized controlled trial was undertaken. Sixty patients with type 2 diabetes with Leriche-Fontaine stage I peripheral arterial disease were randomly assigned to an exercise or placebo group. For 25 weeks, the exercise group underwent treatment comprising 3 exercises at proximal, medium, distal segments of the lower limbs with with of finger feet simultaneously; and the placebo group received sham treatment with disconnected ultrasound equipment. Peripheral arterial disease was determined by evaluating the ankle/brachial index, dermal Doppler flow velocity, blood parameters, cardiovascular risk score, and heart rate during three exercise modalities.

Results: After 25 weeks of treatment, significant differences between groups were found in the following: Dermal Doppler flow velocity (cm/s) in the right foot ($p < 0.040$) and left foot ($p < 0.039$), right ($p < 0.021$) and left ($p < 0.019$) ankle/brachial index ; and fibrinogen ($p < 0.048$), hemoglobin ($p < 0.043$), cholesterol ($p < 0.032$), high-density lipoprotein cholesterol ($p < 0.039$), and HbA1c ($p < 0.046$) values. There was no significant difference in low-density lipoprotein cholesterol values ($p < 0.098$) between the groups.

Conclusion: A program of these three physical therapy modalities on lwer limb with finger feet movements improves ankle/brachial index, dermal Doppler flow velocity, and blood parameters in patients with type 2 diabetes.