tailed information on endocrinology books, visit our website www.jaypeebrothers.com, for detailed information on endocrinology books, visit our website www.jaypeebrothers.com

Diabetology

Under the Aegis of
Diabetes India

Yearbook of Diabetes 2025

Editor-in-Chief
Sujoy Ghosh

JAYPEE

Contents

Section 1: BASIC SCIENCE

Section Editor: Arijit Singha

1. Large-scale Proteomics Improve Prediction of Chronic Kidney Disease in People with Diabetes 1
2. tRNA-derived Fragments are Altered in Diabetes 2
3. Islet Autoantibody Frequency in Relatives of Children with Type 1 Diabetes Who have a Type 2 Diabetes Diagnosis 3
4. Bone Marrow Mesenchymal Stem Cell-derived Exosomal miR-221-3p Promotes Angiogenesis and Wound Healing in Diabetes via the Downregulation of Forkhead Box P1 5
5. The Metabolomic Signature of Weight Loss and Remission in the Diabetes Remission Clinical Trial (DiRECT) 6
6. Multi-omic Prediction of Incident Type 2 Diabetes 8
7. HOMA-IR and the Matsuda Index as Predictors of Progression to Type 1 Diabetes in Autoantibody-positive Relatives 10
8. Zinc Finger BED-type Containing 3 Promotes Hepatic Steatosis by Interacting with Polypyrimidine Tract-binding Protein 1 11
9. Week-long Normoglycemia in Diabetic Mice and Minipigs via a Subcutaneous Dose of a Glucose-responsive Insulin Complex 13

Section 2: EPIDEMIOLOGY

Section Editor: Soham Tarafdar

1. Association between Age at Diabetes Diagnosis and Subsequent Incidence of Cancer: A Longitudinal Population-based Cohort 15
2. Natural History of Type 2 Diabetes in Indians: Time to Progression 17
3. Association of Baseline Factors with Glycemic Outcomes in GRADE: A Comparative Effectiveness Randomized Clinical Trial 19
4. The Difference between Cystatin C- and Creatinine-based Estimated Glomerular Filtration Rate and Risk of Diabetic Microvascular Complications Among Adults With Diabetes: A Population-based Cohort Study 22
5. The Effect of City-level Sugar-sweetened Beverage Taxes on Longitudinal HbA1c and Incident Diabetes in Adults with Prediabetes 24

6. Association of Glucagon-like Peptide-1 Receptor Agonists with Suicidal Ideation and Self-injury in Individuals with Diabetes and Obesity: A Propensity-weighted, Population-based Cohort Study 26
7. Associations between Diabetes and Cancer: A 10-year National Population-based Retrospective Cohort Study 28
8. 5-year Follow-up of the Randomised Diabetes Remission Clinical Trial (DiRECT) of Continued Support for Weight Loss Maintenance in the UK: An Extension Study 31
9. Adiposity and Metabolic Health in Asian Populations: An Epidemiological Study Using Dual-energy X-ray Absorptiometry in Singapore 33
10. Association of Glycaemic Index and Glycaemic Load with Type 2 Diabetes, Cardiovascular Disease, Cancer, and All-cause Mortality: A Meta-analysis of Mega Cohorts of more than 100,000 Participants 36
11. Associations of the Glycaemic Index and the Glycaemic Load with Risk of Type 2 Diabetes in 127,594 People from 20 Countries (PURE): A Prospective Cohort Study 38
12. Daily Low-dose Aspirin and Incident Type 2 Diabetes in Community-dwelling Healthy Older Adults: A Post-hoc Analysis of Efficacy and Safety in the ASPREE Randomised Placebo-controlled Trial 41
13. Early Findings from the NHS Type 2 Diabetes Path to Remission Programme: A Prospective Evaluation of Real-world Implementation 43
14. Food Additive Emulsifiers and the Risk of Type 2 Diabetes: Analysis of Data from the NutriNet-Santé Prospective Cohort Study 46
15. Meat Consumption and Incident Type 2 Diabetes: An Individual-participant Federated Meta-analysis of 1.97 Million Adults with 100,000 Incident Cases from 31 Cohorts in 20 Countries 48

Section 3: COMORBIDITIES

Section Editor: Pritam Biswas

1. Comparative Effectiveness of Aspirin Dosing in Cardiovascular Disease and Diabetes Mellitus: A Subgroup Analysis of the ADAPTABLE Trial 51
2. A Methodological Framework for Meta-analysis and Clinical Interpretation of Subgroup Data: The Case of Major Adverse Cardiovascular Events With GLP-1 Receptor Agonists and SGLT-2 Inhibitors in Type 2 Diabetes 52
3. Effect of Semaglutide on Regression and Progression of Glycemia in People with Overweight or Obesity but without Diabetes in the SELECT Trial 54
4. Semaglutide and Cardiovascular Outcomes by Baseline HbA1c and Change in HbA1c in People with Overweight or Obesity but without Diabetes in SELECT 55
5. Metabolomic Fingerprints of Medical Therapy versus Bariatric Surgery in Patients with Obesity and Type 2 Diabetes: The STAMPEDE Trial 57
6. Cardiovascular and Mortality Outcomes with GLP-1 Receptor Agonists versus Other Glucose-lowering Drugs in Individuals with NAFLD and Type 2 Diabetes: A Large Population-based Matched Cohort Study 58

7. Circulating Metabolomic Markers Linking Diabetic Kidney Disease and Incident Cardiovascular Disease in Type 2 Diabetes: Analyses from the Hong Kong Diabetes Biobank 60
8. Effect of Sodium-glucose Cotransporter-2 Inhibitors on Myocardial Infarction Incidence: A Systematic Review and Meta-analysis of Randomized Controlled Trials and Cohort Studies 61
9. Prediction of New-onset Heart Failure in Patients with Type 2 Diabetes Derived from ALTITUDE and CANVAS 63
10. Impact of Glycaemic Status on the Cardiac Effects of Empagliflozin when Initiated Immediately after Myocardial Infarction: A Post-hoc Analysis of the EMMY Trial 64
11. Impact of Empagliflozin on Insulin Needs in Patients with Heart Failure and Diabetes: An EMPEROR-Pooled Analysis 65
12. Diabetes and Risk of Heart Failure in People with and without Cardiovascular Disease: Systematic Review and Meta-analysis 67
13. Semaglutide in Patients with Obesity-related Heart Failure and Type 2 Diabetes 68
14. Effects of Empagliflozin on Progression of Chronic Kidney Disease: A Prespecified Secondary Analysis from the EMPA-KIDNEY Trial 69
15. Efficacy and Safety of Once-weekly Semaglutide 2.4 mg versus Placebo in People with Obesity and Prediabetes (STEP 10): A Randomised, Double-blind, Placebo-controlled, Multicentre Phase 3 Trial 71
16. Impact of Primary Kidney Disease on the Effects of Empagliflozin in Patients with Chronic Kidney Disease: Secondary Analyses of the EMPA-KIDNEY Trial 73

Section 4: COMPLICATIONS

Section Editor: Abhranil Dhar

1. Mortality in the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE) 76
2. Risk of Diabetic Retinopathy and Diabetic Macular Oedema with Sodium-glucose Cotransporter-2 Inhibitors and Glucagon-like Peptide 1 Receptor Agonists in Type 2 Diabetes: A Real-world Data Study from a Global Federated Database 78
3. Effect of Preceding Drug Therapy on the Renal and Cardiovascular Outcomes of Combined Sodium-glucose Cotransporter-2 Inhibitor and Glucagon-like Peptide-1 Receptor Agonist Treatment in Patients with Type 2 Diabetes and Chronic Kidney Disease 80
4. Comparing Clinical Outcomes in Patients with Type 2 Diabetes Mellitus after Ischaemic Stroke: Sodium-glucose Cotransporter-2 Inhibitors Users versus Non-users. A Propensity Score Matching National Cohort Study 82
5. Uric Acid-lowering Effects of Sodium-glucose Cotransporter 2 Inhibitors for Preventing Cardiovascular Events and Mortality: A Systematic Review and Meta-analysis 84
6. A Meta-analysis of Randomized Controlled Studies Examining the Effects of Sodium-glucose Cotransporter-2 Inhibitors on Peripheral Artery Disease and Risk of Amputations 85

7. Efficacy of Aspirin for Primary Prevention among Adults with High-risk Type 2 Diabetes in the ACCORD Trial 87
8. Glycaemic Control and Macrovascular and Microvascular Outcomes: A Systematic Review and Meta-analysis of Trials Investigating Intensive Glucose-lowering Strategies in People with Type 2 Diabetes 88
9. Incidence and Progression of Diabetic Retinopathy in Patients Treated with Glucagon-like Peptide-1 Receptor Agonists versus Sodium-glucose Cotransporter 2 Inhibitors: A Population-based Cohort Study 90
10. Normoalbuminuria—Is It Normal? The Association of Urinary Albumin within the 'Normoalbuminuric' Range with Adverse Cardiovascular and Mortality Outcomes: A Systematic Review and Meta-analysis 93
11. Comparison of Estimated Glomerular Filtration Rate Change with Sodium-glucose Cotransporter-2 Inhibitors versus Glucagon-like Peptide-1 Receptor Agonists among People with Diabetes: A Propensity-score Matching Study 95
12. Major Adverse Events in Youth-onset Type 1 and Type 2 Diabetes: The SEARCH and TODAY Studies 96
13. Effect of Proteinuria on the Rapid Kidney Function Decline in Chronic Kidney Disease Depends on the Underlying Disease: A Post Hoc Analysis of the BRIGHTEN Study 98
14. Editorials: Diabetic Kidney Disease—Semaglutide Flows into the Mainstream 100
15. A Phase 2 Randomized Trial of Survodutide in MASH and Fibrosis 102
16. Tirzepatide for Metabolic Dysfunction–associated Steatohepatitis with Liver Fibrosis 103
17. Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes 105
18. Effect of SGLT2 Inhibitors on Heart Failure Outcomes and Cardiovascular Death Across the Cardiometabolic Disease Spectrum: A Systematic Review and Meta-analysis 107

Section 5: TYPE 1 DIABETES MELLITUS

Section Editor: Mainak Banerjee

1. Disparities in Continuous Glucose Monitor Use between Children with Type 1 Diabetes Living in Urban and Rural Areas 113
2. Longitudinal Assessment of Pancreas Volume by MRI Predicts Progression to Stage 3 Type 1 Diabetes 114
3. Low-dose Antithymocyte Globulin: A Pragmatic Approach to Treating Stage 2 Type 1 Diabetes 116
4. Exploring Factors that Influence Postexercise Glycemia in Youth with Type 1 Diabetes in the Real World: The Type 1 Diabetes Exercise Initiative Pediatric (T1DEXIP) Study 118
5. A Randomized Comparison of Postprandial Glucose Excursion Using Inhaled Insulin versus Rapid-acting Analog Insulin in Adults with Type 1 Diabetes Using Multiple Daily Injections of Insulin or Automated Insulin Delivery 120
6. Comparing the Glycaemic Outcomes between Real-time Continuous Glucose Monitoring (rt-CGM) and Intermittently Scanned Continuous Glucose Monitoring (isCGM) among Adults and Children with Type 1 Diabetes: A Systematic Review and Meta-analysis of Randomised Controlled Trials 121

7. A First-in-Human, Open-label Phase 1b and a Randomised, Double-blind Phase 2a Clinical Trial in Recent-onset Type 1 Diabetes with AG019 as Monotherapy and in Combination with Teplizumab 123
8. Progression of Type 1 Diabetes is Associated with High Levels of Soluble PD-1 in Islet Autoantibody-positive Children 125
9. Autoimmune Comorbidity in Type 1 Diabetes and its Association with Metabolic Control and Mortality Risk in Young People: A Population-based Study 126
10. The Association of Chronic Complications with Time in Tight Range and Time in Range in People with Type 1 Diabetes: A Retrospective Cross-sectional Real-world Study 128
11. Safety and Efficacy of Teplizumab in the Treatment of Type 1 Diabetes Mellitus: An Updated Systematic Review and Meta-analysis of Randomized Controlled Trials 130
12. Mortality in Type 1 Diabetes Mellitus: A Single Centre Experience from the ICMR–Youth Onset Diabetes Registry in India 132
13. Islet-after-kidney Transplantation versus Kidney Alone in Kidney Transplant Recipients with Type 1 Diabetes (KAIAK): A Population-based Target Trial Emulation in France 134
14. Prediction of Progression to Type 1 Diabetes with Dynamic Biomarkers and Risk Scores 136

Section 6: GESTATIONAL DIABETES MELLITUS AND PREGNANCY IN DIABETES MELLITUS

Section Editor: Indira Maisnam

1. Perinatal Outcomes Associated with Metformin Use during Pregnancy in Women with Pregestational Type 2 Diabetes Mellitus 138
2. Earlier Detection of Gestational Diabetes Impacts on Medication Requirements, Neonatal and Maternal Outcomes 139
3. Prevalence of Gestational Diabetes Mellitus Risk Factors in Singleton Pregnancies Obtained by Assisted Reproductive Technology: An Observational, Retrospective, Real-world Study from a Pregnancy Registry 141
4. Comparing the Different Phenotypes of Diabetes in Pregnancy: Are Outcomes Worse for Women with Young-onset Type 2 Diabetes Mellitus Compared to Type 1 Diabetes? 142
5. Comparing Advanced Hybrid Closed Loop Therapy and Standard Insulin Therapy in Pregnant Women with Type 1 Diabetes (Cristal): A Parallel-group, Open-label, Randomised Controlled Trial 144
6. Early Pregnancy HbA1c as the First Screening Test for Gestational Diabetes: Results from Three Prospective Cohorts 145

Section 7: DRUGS AND THERAPEUTICS

Section Editor: Sunetra Mondal

1. Comparative Effects of Randomized Second-line Therapy for Type 2 Diabetes on a Composite Outcome Incorporating Glycemic Control, Body Weight, and Hypoglycemia: An Analysis of the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE) 148

2. Impact of Canagliflozin on Kidney and Cardiovascular Outcomes by Type 2 Diabetes Duration: A Pooled Analysis of the CANVAS Program and CREDENCE Trials 150
3. Occurrence of Gastrointestinal Adverse Events Upon GLP-1 Receptor Agonist Initiation with Concomitant Metformin Use: A Post Hoc Analysis of LEADER, STEP 2, SUSTAIN-6, and PIONEER 6 151
4. Early-onset Type 2 Diabetes and Tirzepatide Treatment: A Post Hoc Analysis from the SURPASS Clinical Trial Program 153
5. Efficacy and Safety of LX9211 for Relief of Diabetic Peripheral Neuropathic Pain (RELIEF-DPN 1): Results of a Double-blind, Randomized, Placebo-controlled, Proof-of-concept Study 155
6. Glucose-lowering Drugs and Liver-related Outcomes Among Individuals with Type 2 Diabetes: A Systematic Review of Longitudinal Population-based Studies 156
7. Dose-response Effects on HbA1c and Bodyweight Reduction of Survodutide, a Dual Glucagon/GLP-1 Receptor Agonist, Compared with Placebo and Open-label Semaglutide in People with Type 2 Diabetes: A Randomised Clinical Trial 158
8. Subcutaneously Administered Tirzepatide vs Semaglutide for Adults with Type 2 Diabetes: A Systematic Review and Network Meta-analysis of Randomised Controlled Trials 160
9. Ultra-rapid Lispro Improved Postprandial Glucose Control Compared to Insulin Lispro in Predominantly Chinese Patients with Type 1 Diabetes: A Prospective, Randomized, Double-blind Phase 3 Study 162
10. Once-daily Oral Small-molecule Glucagon-like Peptide-1 Receptor Agonist Lotiglipron (PF-07081532) for Type 2 Diabetes and Obesity: Two Randomized, Placebo-controlled, Multiple-ascending-dose Phase 1 Studies 164
11. Effect of Tirzepatide on Body Fat Distribution Pattern in People with Type 2 Diabetes 166
12. Glucagon-like Peptide-1 Receptor Agonist-based Agents and Weight Loss Composition: Filling the Gaps 168
13. Oral or Injectable Semaglutide for the Management of Type 2 Diabetes in Routine Care: A Multicentre Observational Study Comparing Matched Cohorts 169
14. Effectiveness of Switching from Dipeptidyl Peptidase-4 Inhibitor to Oral Glucagon-like Peptide-1 Receptor Agonist in Japanese Participants with Type 2 Diabetes Mellitus: Prospective Observational Study Using Propensity Score Matching 171
15. Inclisiran in Individuals with Diabetes or Obesity: Post Hoc Pooled Analyses of the ORION-9, ORION-10 and ORION-11 Phase 3 Randomized Trials 173
16. Pioglitazone Reduces Serum Ketone Bodies in Sodium-glucose Cotransporter-2 Inhibitor-treated Non-obese Type 2 Diabetes: A Single-centre, Randomized, Crossover Trial 175
17. Are the Cardiovascular Properties of GLP-1 Receptor Agonists Differentially Modulated by Sulfonylureas? Insights from Post-hoc Analysis of EXSCEL 177
18. Tirzepatide 5, 10 and 15 mg versus Injectable Semaglutide 0.5 mg for the Treatment of Type 2 Diabetes: An Adjusted Indirect Treatment Comparison 179
19. Continuous Glucose Monitoring-based Metrics and the Duration of Hypoglycaemia Events with Once-weekly Insulin Icodec versus Once-daily Insulin Glargine U100 in Insulin-naive Type 2 Diabetes: An Exploratory Analysis of ONWARDS 1 181

20. Efficacy and Safety of SGLT2 Inhibitors with and without Glucagon-like Peptide 1 Receptor Agonists: A SMART-C Collaborative Meta-analysis of Randomised Controlled Trials 183
21. Once-weekly Insulin Icodec as Compared to Once-daily Basal Insulins: A Meta-analysis 185
22. Insulin Efsitora versus Degludec in Type 2 Diabetes without Previous Insulin Treatment 186

Section 8: NEWER TECHNOLOGIES

Section Editor: Anirban Sinha

1. Efficacy and Safety of Continuous Glucose Monitoring and Intermittently Scanned Continuous Glucose Monitoring in Patients with Type 2 Diabetes: A Systematic Review and Meta-analysis of Interventional Evidence 189
2. Estimating Glycemia from HbA1c and CGM: Analysis of Accuracy and Sources of Discrepancy 190
3. Relationship between Sensor-detected Hypoglycemia and Patient-reported Hypoglycemia in People with Type 1 and Insulin-treated Type 2 Diabetes: The Hypo-METRICS Study 192
4. Does Fully Closed-loop Automated Insulin Delivery Improve Glycemic Control in Patients with Type 2 Diabetes? A Meta-analysis of Randomized Controlled Trials 193
5. Real Time Continuous Glucose Monitoring in High-risk People with Insulin-requiring Type 2 Diabetes: A Randomised Controlled Trial 195
6. Continuous Glucose Monitoring with Structured Education in Adults with Type 2 Diabetes Managed by Multiple Daily Insulin Injections: A Multicentre Randomised Controlled Trial 196
7. Comparison between a Tubeless, On-body Automated Insulin Delivery System and a Tubeless, On-body Sensor-augmented Pump in Type 1 Diabetes: A Multicentre Randomised Controlled Trial 198
8. Performance of the MiniMed 780G System on Mitigating Menstrual Cycle-dependent Glycaemic Variability 199

Section 9: OTHERS

Section Editor: Nisha Batra

1. Optimal Dose and Type of Physical Activity to Improve Glycemic Control in People Diagnosed With Type 2 Diabetes: A Systematic Review and Meta-analysis 201
2. Suicidal Ideation, Suicide Attempts, and Suicide Deaths in Adolescents and Young Adults with Type 1 Diabetes: A Systematic Review and Meta-analysis 203
3. Individualizing Treatment of Type 2 Diabetes after Metformin: More Insights from GRADE 205
4. Diabetes Management in Detention Facilities: A Statement of the American Diabetes Association 207

5. Dapagliflozin Improves Erectile Dysfunction in Patients with Type 2 Diabetes Mellitus: An Open-label, Non-randomized Pilot Study 209
6. Footwear Fit as a Causal Factor in Diabetes-related Foot Ulceration: A Systematic Review 211
7. Effectiveness and Safety of Empagliflozin: Final Results from the EMPRISE Study 213
8. Impact of the Timing of Metformin Administration on Glycaemic and Glucagon-like Peptide-1 Responses to Intraduodenal Glucose Infusion in Type 2 Diabetes: A Double-blind, Randomised, Placebo-controlled, Crossover Study 215
9. Efficacy and Safety of Oral Semaglutide Monotherapy versus Placebo in a Predominantly Chinese Population with Type 2 Diabetes (PIONEER 11): A Double-blind, Phase IIIa, Randomised Trial 217
10. Comparative Renal Outcomes of Matched Cohorts of Patients with Type 2 Diabetes Receiving SGLT2 Inhibitors or GLP-1 Receptor Agonists Under Routine Care 219
11. Glucagon-like Peptide-1 Receptor Agonists and Risk of Thyroid Cancer: A systematic Review and Meta-analysis of Randomized Controlled Trials 221
12. Beneficial Effect of Oral Semaglutide for Type 2 Diabetes Mellitus in Patients with Metabolic Dysfunction-associated Steatotic Liver Disease: A Prospective, Multicentre, Observational Study 223
13. Fluoroquinolones and the Risk of Severe Hypoglycaemia Among Sulphonylurea Users: Population-based Cohort Study 225
14. Denosumab, for Osteoporosis, Reduces the Incidence of Type 2 Diabetes, Risk of Foot Ulceration and All-cause Mortality in Adults, Compared with Bisphosphonates: An Analysis of Real-world, Cohort Data, with a Systematic Review and Meta-analysis 227
15. The Use of Composite Endpoints in Cardiovascular Outcome Trials for Diabetes: A Review of 22 Randomized Clinical Trials Published Since 2008 229
16. Efficacy, Adherence and Persistence of Various Glucagon-like Peptide-1 Agonists: Nationwide Real-life Data 231
17. Association of Iron Status with All-cause and Cause-specific Mortality in Individuals with Diabetes 233
18. Fair Allocation of GLP-1 and Dual GLP-1–GIP Receptor Agonists 235
19. Intensive Blood-pressure Control in Patients with Type 2 Diabetes 237
20. Type 2 Diabetes in Patients with G6PD Deficiency 239

Index **247**

Section 1: BASIC SCIENCE

Section Editor: Arijit Singha

1. Large-scale Proteomics Improve Prediction of Chronic Kidney Disease in People with Diabetes

Ref: Ye Z, Zhang Y, Zhang Y, Yang S, He P, Liu M, et al. Large-Scale Proteomics Improve Prediction of Chronic Kidney Disease in People With Diabetes. Diabetes Care. 2024;47(10):1757-63.

ABSTRACT

Objective: Chronic kidney disease (CKD) polygenic risk score and a validated clinical risk model [CKD Prediction Consortium (CKD-PC)] will be compared with the predictive ability of a protein risk score for CKD prediction in diabetic patients.

Research design and methods: 2,094 diabetic patients having proteomics and genetic data from the UK Biobank Pharma Proteomics Project who had no prior history of CKD were included in this cohort analysis. A CKD protein risk score comprising 11 proteins was created in the training set (which included 1,047 participants and 117 CKD occurrences) based on almost 3,000 plasma proteins.

Results: 12.1 years was the median follow-up period. The CKD protein risk score was positively correlated with incident CKD [per standard deviation (SD) increment; hazard ratio 1.78; 95% confidence interval (CI) 1.44, 2.20] in the test sample, which included 1,047 patients and 112 CKD incidents. The prediction performance of incident CKD was significantly improved by the CKD protein risk score (C-index increase 0.122; 95% CI 0.071, 0.177) and the CKD-PC risk factors (C-index increase 0.175; 95% CI 0.126, 0.217) when compared to the basic model (age + sex + race, C-index, 0.627; 95% CI 0.578, 0.675). However, there was no significant improvement in the CKD polygenic risk score (C-index increase 0.007; 95% CI 20.016, 0.025).

The continuous 10-year net reclassification (0.199; 95% CI 0.059, 0.299) and 10-year integrated discrimination index (0.041; 95% CI 0.007, 0.083) were both markedly improved by adding the CKD protein risk score to the CKD-PC risk factors. This resulted in the largest C-index of 0.825 (C-index from 0.802 to 0.825; difference 0.023; 95% CI 0.006, 0.044).

Conclusion: The discrimination and reclassification of CKD risk in diabetic individuals was much enhanced by the addition of the CKD protein risk score to a validated clinical risk model.

CRITICAL APPRAISAL

What was Known Prior to this Study?

Chronic kidney disease (CKD) is a significant and increasingly prevalent global health issue, affecting 10% of adults worldwide. Polygenic risk scores, which include sequence variants, have the potential to improve screening and prevention efforts for CKD. However, the clinical applicability of these polygenic risk scores in assessing CKD risk in patients with diabetes requires validation through prospective studies. The potential of proteomic profiling lies in its ability to identify novel biomarkers that may indicate the onset of CKD before it occurs. Some studies have investigated the relationship between various circulating proteins and the risk of CKD progression in individuals with diabetic kidney disease. However, there is a notable lack of research regarding the predictive value of circulating proteins in assessing CKD risk among people with diabetes. The Chronic Kidney Disease Prediction Consortium (CKD-PC) has developed an equation to

JAYPEE BROTHERS

predict the incidence of CKD in individuals with diabetes. Enhancing the validated CKD-PC model by incorporating a panel of multiple protein biomarkers and addressing various pathophysiological pathways of CKD may significantly improve the accuracy of CKD risk prediction—a hypothesis that has not yet been explored.

What this Study Adds?

The study developed and validated a protein risk score for CKD derived from large-scale proteomics. This score serves as a robust and independent predictor of incident CKD in individuals with diabetes. It significantly enhances the ability to discriminate and reclassify CKD risk in diabetic patients, whether used in conjunction with age and sex or when added to an established clinical risk model for CKD.

Limitations of the Study

The UK Biobank is composed primarily of individuals with European ancestry, warranting future investigations to assess the translation of the protein risk score across diverse populations and ethnicities. These proteins are not easily measured in routine clinical chemistry. Further validations outside this cohort would be good to be able to use these as risk protein markers.

Impact on Clinical Practice

Incorporating the CKD protein risk score into clinical practice leads to better risk stratification and earlier prevention for patients with diabetes at risk for developing CKD.

2. tRNA-derived Fragments are Altered in Diabetes

Ref: Ng N, Gibriel HAY, Halang L, Jirström E, Ioana JA, Burke M, et al. tRNA-derived fragments are altered in diabetes. Diabet Med. 2024;41(2):e15258.

ABSTRACT

Aim: Due to its diverse clinical presentation, maternally inherited diabetes and deafness (MIDD), an uncommon form of adult-onset diabetes, can be challenging to diagnose. A new and developing class of small noncoding RNAs (sncRNAs) transfers RNA-derived tiny fragments and shows great potential as serum biomarkers because of their abundance, stability, simplicity of detection, and stress-induced production.

Methods: We examined the amounts of tiRNA 5'ValCAC (both alone and in conjunction with miR-23b-3p) found in serum samples from MIDD, type 1 diabetes, type 2 diabetes, and healthy controls based on small RNA sequencing investigations.

Results: Subjects with MIDD and type 2 diabetes had lower serum levels of 5'ValCAC than controls. Serum levels of miR-23b-3p were higher in individuals with type 2 diabetes than in any other group. The potential of 5'ValCAC and miR-23b-3p as MIDD indicators was demonstrated by Receiver operating characteristic analysis; the combination demonstrated good separation from people with type 2 diabetes.

Conclusion: This is the first study demonstrating that individuals with diabetes had changed tiRNA levels in their serum. Serum biomarkers 5'ValCAC and miR-23b-3p together may be able to distinguish between individuals with MIDD and those with type 2 diabetes.

JAYPEE BROTHERS

CRITICAL APPRAISAL

What was Known Prior to this Study?

Maternally inherited diabetes and deafness (MIDD) is a rare form of adult-onset diabetes (0.5–2.8% of cases) caused by mutations in mitochondrial DNA (mtDNA). The diagnosis of MIDD can be difficult due to phenotypic variability, and diabetes can often be misdiagnosed as type 1 or type 2 diabetes. High-pitched sensorineural hearing loss may not be detected until an audiogram is performed. Therefore, early accessible biomarkers may aid to guide subsequent genetic testing for MIDD. Small noncoding RNAs (sncRNAs) have been identified as potential biomarkers for MIDD, with several studies highlighting miRNAs to be differentially abundant in blood and muscle compared to controls. Transfer RNA-derived small fragments (tsRNAs) are a novel class of sncRNAs derived from transfer RNAs. A subclass of tsRNAs, the so-called tRNA-derived stress-induced RNAs (tiRNAs), is produced by cleavage of tRNAs in their anticodon loop in response to metabolic, hypoxic, or oxidative stress. In the pancreas, tiRNAs 5'HIS-GTG and 5'GLU-GTC have been found to control mitochondrial respiration, β-cell proliferation and insulin secretion. In this study, small RNA-seq analysis of pooled serum samples from MIDD, type 1 diabetes and type 2 diabetes subjects, as well as healthy controls was performed to identify sncRNAs with altered expression.

What this Study Adds?

Serum levels of 5'ValCAC were found to be reduced in subjects with MIDD (mitochondrial diabetes) and type 2 diabetes when compared to control groups. In contrast, individuals with type 2 diabetes had higher serum levels of miR-23b-3p compared to all other subjects. Receiver operating characteristic (ROC) analysis indicated that both 5'ValCAC and miR-23b-3p have potential as biomarkers for MIDD, and their combination shows excellent differentiation from subjects with type 2 diabetes.

Strength of the Study

This report is the first to show altered serum levels of tiRNAs in subjects with diabetes.

Limitations of the Study

Absence of functional studies to determine the biological role of tiRNA in diabetes and small sample size are significant limitations of the study. Presence of hypertension, dyslipidemia, and medications could potentially alter the expression of tiRNA.

Impact on Clinical Practice/Future Scope of Research

Levels of tiRNAs 5'ValCAC and 5'GlyGCC in the serum of MIDD and type 2 diabetes subjects and suggest that the differing expression levels seen here may be associated with reduced skeletal muscle insulin sensitivity. Combined use of 5'ValCAC and miR-23b-3p as serum biomarkers may help differentiate MIDD from type 2 diabetes patients and possibly type 1 diabetes patients.

3. Islet Autoantibody Frequency in Relatives of Children with Type 1 Diabetes Who have a Type 2 Diabetes Diagnosis

Ref: Lewis SJ, Williams CL, Mortimer GL, Oram RA, Hagopian WA, Gillespie KM, et al.; AWAF; BOX Study Group. Islet autoantibody frequency in relatives of children with type 1 diabetes who have a type 2 diabetes diagnosis. Diabet Med. 2024;41(9):e15394.

JAYPEE BROTHERS

ABSTRACT

Aim: The purpose of this study was to assess autoimmune traits in people with a type 2 diagnosis who are related to children with type 1 diabetes.

Methods: The type 1 diabetes genetic risk score (GRS2) and autoantibodies to glutamate decarboxylase 65 (GADA), islet antigen-2 (IA-2A), zinc transporter 8 (ZnT8A), and insulin (IAA) were measured in prediagnosis samples (median 17 months prior to onset) from relatives who were subsequently diagnosed with type 2 diabetes. Fisher's exact and t-tests were used to examine relationships between islet autoantibodies, insulin therapy, and GRS2.

Results: 32 (14%) of the 226 relatives (64% male; mean age at sampling 41 years; mean age at diagnosis 54 years) tested positive for at least one islet autoantibody >10 years prior to diagnosis. Insulin was used to treat around half of them ($n = 15$). Relatives receiving insulin had higher GADA-positivity than relatives not receiving insulin [12/18 (67%) vs. 6/18 (33%), $p < 0.001$]. 13 out of 32 (41%) relatives with autoantibodies had IAA-positivity. Autoantibody-positive relatives had higher GRS2 scores ($p = 0.032$), but there was no conclusive evidence of a treatment-related difference ($p = 0.072$).

Conclusion: This study emphasizes how crucial it is to measure islet autoantibodies, such as IAA, in family members of individuals with type 1 diabetes in order to prevent misdiagnosis.

CRITICAL APPRAISAL

What was Known Prior to this Study?

Earlier study found that children who were newly diagnosed with type 1 diabetes and had a family history of type 2 diabetes exhibited certain phenotypic characteristics typical of type 2 diabetes. However, genome-wide association studies indicate that the underlying causes of these conditions are different. This study focuses on first-degree relatives of individuals with type 1 diabetes who were later diagnosed with type 2 diabetes. The aim of the study was to determine whether these relatives possess immunogenetic features associated with type 1 diabetes.

What this Study Adds?

Distinguishing between type 1 and type 2 diabetes in adults is complex, as clinical features alone cannot accurately classify the type of diabetes. There is ongoing debate among some clinicians about whether all new diabetes cases in individuals under 30 years of age should be referred to secondary care. Recent studies on postdiagnosis type 2 diabetes have identified islet autoantibodies. Notably, there has been a first report documenting prediagnosis islet autoimmunity and genetic risk score (GRS) in samples from relatives who were later diagnosed with type 2 diabetes. The presence of islet autoantibodies, along with a high GRS, can support a diagnosis of adult-onset type 1 diabetes. Testing for islet autoantibodies in family members of individuals with type 1 diabetes could help reduce misclassification in primary diabetes care and inform future testing guidelines.

Strength of the Study

Detection of islet autoantibodies before diabetes onset in relatives of probands with type 1 diabetes.

Limitations of the Study

The sample size for this study is relatively small when compared to other population studies. Additionally, it did not include analyses of C-peptide, hemoglobin A1c (HbA1c), or body mass index (BMI). Previous research has indicated that BMI may influence islet autoimmunity in individuals with type 2 diabetes, noting that individuals who are GADA-positive tend to have a lower BMI than those who are GADA-negative. Our sample population was predominantly of White European descent. The study also examined the use of GRS in relatives of individuals with

JAYPEE BROTHERS

type 1 diabetes. By definition, these relatives are expected to have a higher type 1 diabetes GRS compared to the general population.

Impact on Clinical Practice/Future Research

This study has revealed that some individuals may have been misdiagnosed with type 2 diabetes, even though they are relatives of children with type 1 diabetes. These individuals were clearly positive for autoantibodies and/or had a high GRS prior to their type 2 diabetes diagnosis. Further research is necessary to develop a more specific and sensitive method for clinicians to accurately identify type 1 diabetes in adults.

4. Bone Marrow Mesenchymal Stem Cell-derived Exosomal miR-221-3p Promotes Angiogenesis and Wound Healing in Diabetes via the Downregulation of Forkhead Box P1

Ref: Qiu ZY, Xu WC, Liang ZH. Bone marrow mesenchymal stem cell-derived exosomal miR-221-3p promotes angiogenesis and wound healing in diabetes via the downregulation of forkhead box P1. Diabet Med. 2024;41(9):e15386.

ABSTRACT

Aim: Diabetes patients may develop nonhealing ulcers as a result of impaired wound healing. This work is to explore the mechanism of bone marrow mesenchymal stem cells (BMSCs)-isolated exosomal miR-221-3p in angiogenesis and diabetic wound healing since BMSC exosomes can aid in wound healing.

Methods: Human umbilical vein endothelial cells (HUVECs) were exposed to high glucose (HG) in order to simulate diabetes in vitro. Transmission electron microscopy (TEM), western blot analysis, and dynamic light scattering (DLS) were used to identify the exosomes that were isolated from BMSCs. Alizarin red, alkaline phosphatase (ALP), and oil red O staining were used to evaluate the capacity to distinguish BMSCs. Using confocal microscopy, the capacity to internalize exosomes labeled with PKH26 was evaluated. Scratch, MTT, and tube formation tests were used independently to assess migration, cell viability, and angiogenesis. Western blotting or quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) were used to analyze the amounts of miRNA and protein. The dual-luciferase reporter, ChIP, and RIP assays were used to ascertain the connection between miR-221-3p, FOXP1, and SPRY1.

Results: After being successfully extracted from BMSCs, exosomal miR-221-3p was introduced into HUVECs. Exosomal miR-221-3p isolated from BMSCs decreased the angiogenesis, cell survival, and migration of HUVECs, which were reported to be suppressed by HG. FOXP1 has the potential to transcriptionally upregulate SPRY1, and by downregulating SPRY1, FOXP1 silencing reversed the inhibition of HG-stimulated angiogenesis, cell survival, and migration in HUVECs. Conversely, miR-221-3p specifically targeted FOXP1, and the beneficial effect of exosomal miR-221-3p on HUVEC angiogenesis was counteracted by FOXP1 overexpression.

Conclusion: Through the FOXP1/SPRY1 axis, exosomal miR-221-3p that was isolated from BMSCs stimulated angiogenesis in diabetic wounds. Additionally, the results of this study can offer fresh perspectives on diabetes prevention techniques.

JAYPEE BROTHERS

CRITICAL APPRAISAL

What was Known Prior to this Study?

Diabetic foot ulcer (DFU) is a debilitating complication of chronic hyperglycemia and often leads to significant morbidity and mortality. Though some interventions can slow the progression of diabetic wound healing, the persistent nature of these wounds presents a significant clinical challenge. A key factor in impaired healing is the inhibition of angiogenesis, which is often observed in diabetic patients. Surgical interventions may restore peripheral blood flow, but their effectiveness can be limited. Therefore, promoting angiogenesis is essential for advancing the treatment of diabetic wounds. Bone marrow mesenchymal stem cells (BMSCs) are multipotent stem cells capable of self-renewal and differentiation into various cell types. A recent study highlighted the therapeutic benefits of using BMSCs for tissue repair and regeneration. Although BMSC-based wound healing therapies have shown promising results in preclinical studies, they are still in the early stages of clinical trials. Furthermore, the molecular mechanisms underlying the role of BMSCs in diabetic wound healing require further investigation. Exosomes are extracellular vehicles (EVs) with a diameter of 30–150 nm that can transport RNAs to target cells, where they exert various effects. Additionally, BMSC-derived exosomes have demonstrated beneficial effects on diabetic wounds by delivering RNAs. Moreover, miR-221-3p is present in exosomes secreted by BMSCs and BMSC-derived exosomal miR-221-3p has been shown to alleviate asthma; however, it remains to be determined whether BMSC-derived exosomes can promote wound healing in diabetes by containing miR-221-3p. In this study, the role of BMSC-derived exosome on angiogenesis was evaluated.

What this Study Adds?

Exosomes containing miR-221-3p isolated from BMSCs alleviated HG-mediated inhibition of angiogenesis in human umbilical vein endothelial cells (HUVECs). miR-221-3p could directly sponge FOXP1 and downregulates SPRY1. BMSCs-isolated exosomal miR-221-3p promoted wound healing in diabetic mice by targeting FOXP1/SPRY1 axis.

Limitations of the Study

The clinical samples were not included in this study, which may limit the applicability of the findings to real-world scenarios. Furthermore, additional mechanisms underlying exosomal miR-221-3p in diabetic wounds have not yet been investigated.

Impact on Clinical Practice/Future Scope

The significant findings of this study could facilitate the development of effective therapies for curing diabetic foot in the clinical setting.

5. The Metabolomic Signature of Weight Loss and Remission in the Diabetes Remission Clinical Trial (DiRECT)

Ref: Corbin LJ, Hughes DA, Bull CJ, Vincent EE, Smith ML, McConnachie A, et al. The metabolomic signature of weight loss and remission in the Diabetes Remission Clinical Trial (DiRECT). Diabetologia. 2024;67(1):74-87.

ABSTRACT

Aim/Hypothesis: A consistent metabolomic signature of type 2 diabetes and overweight has been shown using high-throughput metabolomics technologies in a range of experimental types. Little research has been done on how much weight loss and diabetes remission can reverse these metabolomic

JAYPEE BROTHERS

abnormalities. Our goal was to describe the metabolomic effects of a weight-loss program in people with type 2 diabetes.

Methods: 574 fasting serum samples (n = 298) obtained from an ongoing randomized controlled trial (RCT) [the Diabetes Remission Clinical Trial (DiRECT)] were analyzed. Participants in the trial were randomly allocated (1:1) to treat patients with type 2 diabetes with either a weight management program (intervention) or best-practice care according to guidelines (control). Here, samples obtained at baseline and after a year were subjected to metabolomics analysis using both untargeted mass spectrometry (MS) and targeted 1H-nuclear magnetic resonance (^{1}H-NMR) spectroscopy. To assess how the intervention affected metabolite levels, multivariable regression models were built.

Results: The intervention was linked to increases in sphingolipids, plasmalogens, and metabolites involved with fatty acid metabolism and decreases in sugars, low-density lipoprotein (LDL) triglycerides, and branched-chain amino acids (Holm-corrected $p < 0.05$). Those who achieved diabetic remission experienced higher reductions in glucose, fructose, and mannose than those who did not, among those who lost >9 kg between baseline and 12 months.

Conclusion/Interpretation: We have described the metabolomic impacts of a comprehensive weight-management program that has been demonstrated to result in both diabetes remission and weight loss. It seems that a significant amount of the metabolome is changeable. Change patterns were mostly and remarkably at odds with disturbances previously linked to the onset of type 2 diabetes.

CRITICAL APPRAISAL

What was Known Prior to this Study?

In the study of type 2 diabetes, the relationship among risk factors, intermediate metabolic phenotypes, and the disease has prompted interest in using metabolomics to clarify the biological mechanisms involved. Research has consistently identified a strong metabolomic signature related to both prevalent and newly diagnosed type 2 diabetes. Given the overlap in metabolomic profiles between type 2 diabetes and its precursors—overweight/obesity and insulin resistance—many changes observed in diagnosed individuals may also influence disease development. However, it remains unclear whether these changes are a systemic 'downstream' response to high glucose or an "upstream" response to excess adiposity.

To enhance the understanding, it is essential to assess the metabolomic response to disease remission following interventions. Weight loss has shown significant efficacy in managing type 2 diabetes, with sustained metabolic benefits lasting up to a decade. However, concerns about the reliability of existing metabolomics studies, often due to small sample sizes and single-arm designs, warrant further investigation. The study analyzed samples of the pivotal randomized controlled trial (RCT)—the Diabetes Remission Clinical Trial (DiRECT)—to characterize the metabolomic profile associated with this intensive weight management intervention.

What this Study Adds?

Baseline characteristics were similar when comparing the intervention group with the control group. Participants at intervention group lost ~10 kg weight at the end of 12 months. The intervention was associated with a decrease in branched-chain amino acids, sugars, and low-density lipoprotein (LDL) triglycerides, along with an increase in sphingolipids, plasmalogens, and metabolites related to fatty acid metabolism (Holm-corrected $p < 0.05$). Under a conservative correction for multiple testing, 26% of nuclear magnetic resonance (NMR)-derived metabolites and 12% of mass spectrometry (MS)-derived metabolites were altered by the intervention. This suggests that a sizeable proportion of metabolite changes in type 2 diabetes are modifiable. The changes were evident many weeks after the conclusion of the weight-loss phase of the intervention, indicating sustained benefits to health.

JAYPEE BROTHERS

Major Strengths of the Study

The study utilized samples and clinical data from a relatively large cluster-randomized trial, which had a well-matched control group compared to existing literature. By measuring metabolites both at baseline and after 12 months, the analysis was strengthened. Additionally, the use of two complementary metabolomics platforms expanded the overall coverage of the metabolome beyond what has been previously evaluated.

Limitations of the Study

The MS data are semiquantitative meaning that these findings require further validation using targeted techniques to allow absolute quantification. It is a challenge to attribute those changes to specific elements of the intervention (e.g., to fat loss per se or "upstream" changes in diet). Effects of weight loss on metabolome should be interpreted cautiously and should be validated in larger cohort.

Impact on Clinical Practice/Future Research Scope

Findings suggest excess weight is upstream of many previously reported metabolomic changes connected with type diabetes mellitus and that energy restriction is an effective way of improving multiple metabolic health signals.

6. Multi-omic Prediction of Incident Type 2 Diabetes

Ref: Carrasco-Zanini J, Pietzner M, Wheeler E, Kerrison ND, Langenberg C, Wareham NJ. Multi-omic prediction of incident type 2 diabetes. Diabetologia. 2024;67(1):102-12.

ABSTRACT

Aim/Hypothesis: One important component of population-level prevention methods is the identification of individuals who are at high risk of developing type 2 diabetes. Prior research has assessed the predictive value of omics measures, including proteins, metabolites, and polygenic scores, but has done so in isolation. It is unknown how much better integrated omics biomarkers can be than the existing clinical standard models. Testing the predictive capabilities of the genome, proteome, metabolome, and clinical biomarkers in conjunction with well-established clinical prediction models for type 2 diabetes was the goal of this work.

Methods: In a prospective, nested type 2 diabetes case-cohort study (n = 1,105, incident type 2 diabetes cases = 375) with 10,792 person-years of follow-up, we created sparse interpretable prediction models. We used least absolute shrinkage and selection operator (LASSO) regression to select from 5,759 features across the genome, proteome, metabolome, and clinical biomarkers. We used a clinical model that included factors from the Cambridge Diabetes Risk Score and hemoglobin A1c (HbA1c) to examine the predictive ability of omics-derived predictors.

Results: The top 10 proteins by themselves performed the best among single omics prediction models that lacked clinical risk factors {concordance index (C index) = 0.82 [95% confidence interval (CI) 0.75, 0.88]}, indicating that the proteome is the most informative single omic layer when clinical data is lacking. Nonetheless, the top 10 variables across several omic layers produced the greatest increase in type 2 diabetes incidence prediction over and above the clinical model [C index = 0.87 (95% CI 0.82, 0.92), Δ C index = 0.05, p = 0.045].

The top 10 omic features also showed improvement in those with HbA1c < 42 mmol/mol (6.0%), the prediabetes threshold [C index = 0.84 (95% CI 0.77, 0.90), Δ C index = 0.07, p = 0.03], the group for which prediction would be most helpful because current clinical guidelines do not target them for preventative interventions. The primary factor in this subgroup's increase in prediction was the type 2

JAYPEE BROTHERS

diabetes polygenic risk score, which also produced a similar improvement in performance when added to the clinical model alone [C index = 0.83 (95% CI 0.75, 0.90), Δ C index = 0.06, p = 0.002]. However, during a 20-year period, people with high polygenic risk in this group had only about half the absolute risk for type 2 diabetes compared to those with prediabetes.

Conclusion/Interpretation: Omic methods improved incident type 2 diabetes prediction by a small amount. Even those with a high polygenic burden in that cohort had a low absolute risk of type 2 diabetes, despite the fact that a polygenic risk score does improve prediction in those whose HbA1c falls within the normoglycemic range, the group in whom prediction would be most helpful. This implies that the implementation of targeted population-based genetic screening for preventative interventions may not be as feasible as it seems.

CRITICAL APPRAISAL

What was Known Prior to this Study?

Considering the burden of type 2 diabetes mellitus across the world, it is critically important to identify at risk people of development of diabetes. Several risk scores based on patient-derived data are available and they perform well to predict incident diabetes mellitus particularly in people with high-risk group. In addition, blood-based biomarkers [hemoglobin A1c (HbA1c), lipid profiles, uric acid] have been shown to improve the predictive model. Genome-wide association studies (GWAS) have identified hundreds of genetic risk variants; however, genome-wide polygenic risk sores (PRSs) have not shown clinically meaningful improvement over and above the simple clinical models. Integrating the multiomics (proteomics, metabolomics, clinical biomarkers, and genomics) may be helpful to improve the prediction of incident type 2 diabetes mellitus.

What this Study Adds?

It was a case-cohort prospective study which included 1,105 individuals without diabetes mellitus at baseline between 40 and 79 years of age and followed up for 10 years for development of diabetes mellitus. Genome-wide genotyping was performed using the Affymetrix UK Biobank Axiom Array. The Cambridge Diabetes Risk Score was used as clinical predictive score in addition to HbA1c. The study observed that combination of different omics layers achieved the largest improvement in predictive performance over a standard clinical score. Type 2 diabetes mellitus polygenic risk score accounted for the most of the improvement in in predictive performance in individuals without prediabetes. However, the absolute risk of type 2 diabetes mellitus without prediabetes with a high polygenic burden was low.

Major Strengths of the Study

Comprehensive case ascertainment and virtually complete follow-up among deeply phenotyped participants.

Limitations of the Study

The study included participants of European ancestry, limiting the generalizability of results across populations of different ethnic backgrounds. The technology used for proteomics profiling relies on preserved protein structure for recognition by the affinity reagents, meaning that protein-altering variants could lead to biased measurements. External replication of results is currently not possible due to the unique depth of information incorporated in these analyses.

Impact on Clinical Practice/Scope of Future Research

Whether society deems it acceptable to offer preventative interventions to individuals at half the risk of groups for whom interventions are now routinely offered is an economic and political decision.

JAYPEE BROTHERS

7. HOMA-IR and the Matsuda Index as Predictors of Progression to Type 1 Diabetes in Autoantibody-positive Relatives

Ref: Petrelli A, Cugnata F, Carnovale D, Bosi E, Libman IM, Piemonti L, et al. HOMA-IR and the Matsuda Index as predictors of progression to type 1 diabetes in autoantibody-positive relatives. Diabetologia. 2024;67(2):290-300.

ABSTRACT

Aim/Hypothesis: We evaluated the potential correlation between type 1 diabetes stage transitions and the Matsuda Index and HOMA-IR.

Methods: Relatives of people with type 1 diabetes (n = 6,256) who tested positive for autoantibody (AAb) were examined. After adjusting for measures of insulin secretion, Index60, and insulinogenic index (IGI), associations between insulin resistance indicators (HOMA-IR) and insulin sensitivity indicators (Matsuda Index) and body mass index percentile (BMIp) and age were evaluated. To find out if tertiles of HOMA-IR and Matsuda Index predicted progression to Stage 3 [diabetes according to the World Health Organization/American Diabetes Association (WHO/ADA) criteria], from Stage 1 to Stage 2 (≥2 AAbs with dysglycemia), and from Not Staged (<2 AAbs) to Stage 1 (≥2 AAbs and normoglycemia), Cox regression was employed.

Results: The Matsuda Index (inverse) and HOMA-IR (positive) were strongly correlated with BMIp and baseline age ($p < 0.0001$). After controlling for Index60, moving from Stage 1 to Stage 2 was linked to lower Matsuda Index and higher HOMA-IR [HOMA-IR: hazard ratio (HR) 1.71, $p < 0.0001$; Matsuda Index, HR 0.40, $p < 0.0001$], just as moving from Stages 1 or 2 to Stage 3 was linked to lower Matsuda Index and higher HOMA-IR (HOMA-IR: HR 1.98, $p < 0.0001$; Matsuda Index: HR 0.46, $p < 0.0001$). In the absence of adjustments, the correlations between the progression to Stage 3 and the HOMA-IR were inverse, while the Matsuda Index was positive. However, the directionality changed when adjustments were made. The results were comparable when Index60 was substituted with IGI.

Conclusion/Interpretation: After accounting for insulin secretion, the Matsuda Index shows a decrease in progression to Stages 2 and 3 of type 1 diabetes, while the HOMA-IR shows an increase. Insulin secretion indicators seem useful for analyzing correlations between the Matsuda Index or HOMA-IR and the development of type 1 diabetes in families with AAb.

CRITICAL APPRAISAL

What was Known Prior to this Study?

Type 1 diabetes mellitus (DM) is a heterogeneous disorder characterized by autoimmune-mediated beta cell dysfunction leading to deficiency of insulin secretion. Depending upon the presence or absence of islet auto-antibody (Ab) and/or dysglycemia, type 1 DM has three stages, "Not staged"—Ab < 2 and normal glucose tolerance, "Stage 1"—Ab ≥ 2 and normal glucose tolerance, and "Stage 2"—Ab ≥ 2 and dysglycemia. The relative importance of the staging lies in the prevention of the disease. Notably, the rising incidence of obesity in children often poses significant difficulties in making the diagnosis. Furthermore, excess weight gain itself increases the risk of developing type 1 DM. It is important to know whether insulin resistance and insulin sensitivity are possible factors of type 1 DM development. HOMA-IR and Matsuda index are well-validated tool for insulin resistance and insulin sensitivity, respectively. However, deficient insulin secretion in Ab+ relatives of type 1 DM may

JAYPEE BROTHERS

be limiting factor to calculate the above two index. Having said that, adjustment of insulin secretion may be useful. Several studies have documented the insulinogenic index (IGI) and Index60 as surrogate markers of insulin secretion in Ab+ relatives. In this study the HOMA-IR and Matsuda Index, which were adjusted by IGI and Index60, were assessed to characterize the pathogenesis of type 1 DM.

What this Study Adds?

First- and second-degree relatives of individuals with type 1 diabetes were enrolled into the TrialNet Pathway to Prevention (TNPTP) study at the international clinical centers of the TrialNet network. All participants were screened for islet autoantibodies to glutamic acid decarboxylase (GAD) (GADA), insulin (microinsulin antibody assay, mIAA), and IA-2 (IA-2A). If any of these were positive in screening, ZnT8A and ICA were also tested. Participants identified as autoantibody positive, as well as a small subset of those autoantibody negative, were monitored with autoantibody testing, hemoglobin A1c (HbA1c) and an oral glucose tolerance test (OGTT) at 6- or 12-month intervals. A total of n = 6,256 relatives were included in this study, n = 4,459 < 18 years old and n = 1,797 ≥ 18 years old. Estimation of insulin resistance with HOMA-IR and insulin sensitivity with the Matsuda Index was obtained from OGTT data. Beta cell function was measured from OGTTs using Index60, and the IGI. The study found that transitioning from Stage 1 to Stage 2 and progression to Stage 3 of type 1 diabetes was associated with increased levels of HOMA-IR and reduced levels of Matsuda Index, only when adjusted for insulin secretion. Importantly, adjustments with indicators of insulin secretion such as Index60 and IGI appear necessary. The association with HOMA-IR went from inverse to positive, while the association with Matsuda Index went from positive to inverse.

Major Strengths of the Study

This study used the novel approach of adjusting for insulin secretion in assessing whether insulin resistance and insulin sensitivity, indicated by HOMA-IR and the Matsuda Index, respectively, are factors involved in the progression toward type 1 diabetes.

Limitations of the Study

Participants were retrospectively selected in the study. HOMA-IR and Matsuda Index measurements used in this analysis have not been validated for AAb+ populations.

Implications of the Findings for the Clinicians

Insulin resistance play significant role in the progression of type 1 DM.

Scope of Future Research

Targeting insulin resistance to delay the progression of type 1 DM.

8. Zinc Finger BED-type Containing 3 Promotes Hepatic Steatosis by Interacting with Polypyrimidine Tract-binding Protein 1

Ref: Wu Y, Yang M, Wu SB, Luo PQ, Zhang C, Ruan CS, et al. Zinc finger BED-type containing 3 promotes hepatic steatosis by interacting with polypyrimidine tract-binding protein 1. Diabetologia. 2024;67(10):2346-66.

JAYPEE BROTHERS

ABSTRACT

Aim/Hypothesis: It is generally known that type 2 diabetes mellitus, insulin resistance, and the metabolic syndrome are all related to metabolic dysfunction-associated steatotic liver disease (MASLD). Although type 2 diabetes mellitus and the metabolic syndrome have been associated with zinc finger BED-type containing 3 (ZBED3), its function in MASLD is yet unknown. Our goal in this study was to look at ZBED3's role in relation to MASLD.

Methods: ZBED3 expression levels were measured in cellular and animal models of MASLD as well as in MASLD patients. The function of ZBED3 in MASLD was examined in vitro and in vivo using a cellular model of MASLD produced by nonesterified fatty acid (NEFA) and an animal model of MASLD induced by a high-fat diet (HFD), respectively. Lentiviral infection or adeno-associated virus tail-vein injection enhanced ZBED3 expression. Bioinformatics analysis and RNA-seq were used to investigate the mechanisms by which ZBED3 regulates lipid accumulation.

Co-immunoprecipitation and LC-MS/MS were used to examine the molecular mechanisms by which ZBED3 regulates the sterol regulatory element binding-protein 1c (SREBP1c), as the results of these next-generation transcriptome sequencing studies showed that ZBED3 controls SREBP1c (also known as SREBF1; a gene involved in fatty acid de novo synthesis).

Results: In this investigation, we discovered that ZBED3 was markedly elevated in the livers of MASLD patients and MASLD animal models. In vitro, NEFA-induced triglyceride buildup in hepatocytes was facilitated by ZBED3 overexpression. Moreover, ZBED3 overexpression in hepatocytes accelerated hepatic steatosis. On the other hand, resistance to HFD-induced hepatic steatosis was the outcome of ZBED3 deletion specific to hepatocytes. In order to control SREBP1c mRNA stability and alternative splicing, ZBED3 mechanistically interacts directly with polypyrimidine tract-binding protein 1 (PTBP1) and influences its binding to the SREBP1c mRNA precursor.

Conclusion/Interpretation: According to this study, ZBED3 is a key regulator of the development of MASLD and encourages hepatic steatosis.

Data availability: RNA-seq data have been deposited in the NCBI Gene Expression Omnibus (www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE231875). MS proteomics data have been deposited to the ProteomeXchange Consortium via the iProX partner repository (https://proteomecentral.proteomexchange.org/cgi/GetDataset?ID=PXD041743).

JAYPEE BROTHERS

CRITICAL APPRAISAL

What was Known Prior to this Study?

Currently metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common liver disease affecting ~25% of adult population in the world. It is the second most common cause for liver transplantation in the United States. Overall, the pooled prevalence of MASLD in India is 38%. Notably, MASLD is a spectrum disorder ranging from simple steatosis to hepatocellular carcinoma, characterized by accumulation of triglyceride in liver. Hepatic de novo lipogenesis (DNL) is one of the predominant contributing factors of triglyceride accumulation in hepatocytes. Notably, DNL is upregulated in patients with MASLD, in addition, it is independent of adiposity, intrahepatic triglyceride and circulating lipids level. Sterol regulatory element-binding protein-1c (SREBP1c) is the main transcriptional regulator involved in DNL. While protein cleavage, phosphorylation and ubiquitination of *SREBP1c* are well documented, post-transcriptional regulation of alternative splicing of SREBP1c remains unexplored. The RNA-binding protein polypyrimidine tract-binding protein 1 (PTBP1) binds to mRNA sequence of *SREBP1c* and enhance the stability of *SREBP1c* mRNA. Zinc finger BED-type containing 3 (ZBED3) is a member of the zinc finger protein

superfamily and studies have demonstrated ZBED3 level is significantly elevated in insulin resistance, type 2 diabetes mellitus and metabolic syndrome. Furthermore, ZBED3 level is correlated with HOMA, body mass index (BMI) and triglyceride levels, which implies that ZBED3 might be involved in the progression of MASLD. This study was done to explore the role of ZBED3 in hepatic steatosis as well as interaction of ZBED3 with the alternative splicing of *PTBP1*and *SREBP1c* mRNA.

What this Study Adds?

ZBED3 is upregulated in the livers of individuals with steatosis as compared to without steatosis. Similar observation was documented in three animal models. ZBED3 overexpression promoted nonesterified fatty acid (NEFA)-induced triglyceride accumulation in hepatocytes. Furthermore, ZBED3 directly interacts with PTBP1 and affects its binding with *SREBP1c* mRNA precursor to regulate *SREBP1c* mRNA stability and alternative splicing.

Limitations of the Study

The study found elevated ZBED3 levels in individuals with MASLD in only a small selection of human liver samples, and the clinical generalizability of this finding remains to be explored.

Impact on Clinical Practice/Future Research

Elucidating the mechanisms of aberrant RNA splicing could provide therapeutic *targets for diseases*. PTBP1 may provide a good therapeutic target for MASLD.

9. Week-long Normoglycemia in Diabetic Mice and Minipigs via a Subcutaneous Dose of a Glucose-responsive Insulin Complex

Ref: Zhang J, Wei X, Liu W, Wang Y, Kahkoska AR, Zhou X, et al. Week-long normoglycaemia in diabetic mice and minipigs via a subcutaneous dose of a glucose-responsive insulin complex. Nat Biomed Eng. 2024;8(10):1214-25.

ABSTRACT

Insulin formulations that respond to glucose levels can improve their therapeutic effectiveness and decrease the frequency of administration. However, developing single-dose formulations that provide both sustained and glucose-responsive insulin release has been difficult. This research introduces an innovative glucose-responsive formulation for subcutaneous injection that reduces fibrous capsule formation and sustains normal blood glucose levels with minimal risk of hypoglycemia in mice and minipigs with type 1 diabetes for up to seven days. The formulation consists of recombinant human insulin modified with gluconic acid, which strongly binds to poly-L-lysine that has been altered with 4-carboxy-3-fluorophenylboronic acid. This binding occurs through glucose-responsive phenylboronic acid-diol complexation and electrostatic attraction. In the presence of elevated glucose concentrations, the phenylboronic acid groups rapidly bind to glucose, disrupting the complex and reducing the positive charge density of the polymers, thus facilitating insulin release. The encouraging therapeutic performance of this long-acting single-dose formulation suggests the need for further evaluation and clinical translation studies.

JAYPEE BROTHERS

CRITICAL APPRAISAL

What was Known Prior to this Study?

It has been over a century since the discovery of insulin, a pivotal advancement that has transformed diabetes from a condition characterized by significant morbidity and mortality into a manageable chronic illness. Currently, insulin therapy is advancing toward the objective of closely mimicking physiological endogenous insulin profiles, aided by the development of rapid and long-acting insulin formulations, continuous glucose monitoring systems, and hybrid closed-loop systems. Despite these advancements, many individuals living with diabetes continue to experience unmet insulin needs, resulting in prolonged periods of blood glucose levels that fall outside the recommended targets. Noteworthy innovations aimed at enhancing insulin therapy include the engineering of insulins that primarily target the liver, as well as the creation of glucose-responsive insulins (GRIs). These insulins activate when blood glucose levels increase and remain inactive when levels are within the normal range. By mimicking beta-cell function, GRIs release insulin as needed, thereby improving time spent within the target glucose range and decreasing the risks of hypoglycemia and hyperglycemia for those managing diabetes. Particularly relevant is the emergence of a new type of subcutaneously administered therapy.

What this Study Adds?

The authors conducted an evaluation of the GRI conjugate to determine its ability to meet both prandial and basal insulin needs through laboratory assessments and preclinical studies involving mouse and minipig models. The performance of this GRI was also tested in three diabetic minipigs, which closely resemble human physiological characteristics. The results indicated that the GRI maintained its effectiveness in controlling blood glucose levels for a week and showed improved efficacy compared to daily insulin glargine injections. Overall, these findings suggest that this GRI formulation may have clinical potential as a basal insulin. In both the mouse and minipig studies, minimal hypoglycemia was observed, and the insulin complex exhibited low toxicity with no significant formation of fibrous capsules.

Limitations of the Study

The Glucose Response Index must demonstrate responsiveness to a specific range of glucose levels, as this is necessary for effectively maintaining blood glucose in humans. However, the available in vivo studies do not clearly show that it meets this requirement. Additionally, it would be helpful to compare their Glucose Response Index formulation with the new weekly formulations currently in development, particularly regarding the burden of care on patients and the control of glucose levels. Long-term safety data is also needed.

Impact on Clinical Practice/Future Scope of Research

The study contributes to the expanding research on GRIs and presents a proof of concept for a biodegradable insulin complex formulation. This formulation releases insulin in a glucose-responsive manner, demonstrated long-term efficacy in vivo, and appeared to have minimal toxicity. However, further studies are necessary before this agent can be considered a viable option for human use.

JAYPEE BROTHERS

for detailed information on endocrinology books, visit our website www.jaypeebrothers.com, for detailed information on endocrinology books, visit our website www.jaypeebroth

Yearbook of Diabetes 2025

Salient Features

- The "*Yearbook of Diabetes 2025*" is a collection of carefully chosen articles from various peer-reviewed journals published over the last 1 year.
- Current topics are included to ensure that clinicians are fully up to date with the latest developments in the field.
- The book has been divided into nine sections covering Basic Science, Epidemiology, Comorbidities, Complications, Type 1 Diabetes Mellitus, Gestational Diabetes Mellitus and Pregnancy in Diabetes Mellitus, Drugs and Therapeutics, Newer Technologies, and others.
- Authors have attempted to provide background information on what was already known, what the study added in terms of medical knowledge, and the take-home message for the physician.
- Many articles are supported with detailed references for further reading.
- It is an excellent resource for physicians, diabetologists, and postgraduate students.

Printed in India

Available at all medical bookstores or buy online at www.ejaypee.com

JAYPEE BROTHERS
Medical Publishers (P) Ltd.
EMCA House, 23/23-B, Ansari Road,
Daryaganj, New Delhi - 110 002, INDIA
www.jaypeebrothers.com

Join us on facebook.com/JaypeeMedicalPublishers
Follow us on instagram.com/JaypeeMedicalPublishers

Shelving Recommendation
DIABETOLOGY

ISBN 978-93-6616-193-8