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PE130 Basic & translational diabetes research

Exosomes from mesenchymal-stem cells ameliorate diet-induced metabolic dysfunction in mice through enhancing actions of FGF21 and adiponectin and modulating gut microbiota

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Objective: Recent studies have reported the beneficial impacts of exosomes derived from mesenchymal stem cells in preventing or treating metabolic disorders. In the present study, we aim to elucidate the associated specific mechanisms using exosomes derived from human umbilical cord Wharton's jelly mesenchymal stem cells (hWJMSCs) against adiposity and insulin resistance in high-fat diet (HFD)-induced obese mice.

Methods: Six-week-old C57BL/6J male mice on 60%kcal fat diet were injected with hWJMSC-derived exosomes for 11 weeks. The effect of exosome treatment was determined through analyses of body and tissue weight, glucose tolerance, blood lipid profile, and histological tissue features. To explore the molecular mechanisms underlying the effect, real-time PCR, ELISA, and western blotting were used to examine mRNA and protein expression, and NGS on fecal samples was performed.

Results: HFD-fed mice treated with hWJMSC-derived exosomes exhibited significantly enhanced gut barrier integrity, consequently restoring immune homeostasis in the liver and adipose tissues. Treatment of exosomes also significantly restored lipid metabolism, thereby reducing lipotoxicity-induced ER stress, which led to alleviated hepatic and adipose fat accumulation and chronic tissue inflammation. Additionally, hWJMSC-derived exosomes promoted non-shivering thermogenic capacity of adipose tissues. This effect was associated with increased expression of adiponectin and its receptors, as well as fibroblast growth factor (FGF21) and its receptors, leading to the subsequent activation of the AMPK-SIRT1-PGC-1α pathway. The alpha diversity of fecal microbiota was improved by exosome administration, accompanied by the increased abundance of *Clostridia* and decreased alphaproteobacterial population.

Conclusion: Our findings suggest that the improvement of metabolic dysfunctions in exosome-treated HFD-fed mice is linked to the activation of FGF21-adiponectin axis, and to the alteration of microbiota composition. These results shed light on the molecular mechanisms by which hWJMSC-derived exosomes mitigate HFD-induced dysregulation of glucose and lipid homeostasis, positioning them as a promising candidate for the development of therapeutics for metabolic disorders.

PE131 Basic & translational diabetes research

Exploring Indonesian phytochemicals as DPP-IV inhibitors for type II diabetes mellitus therapy: in silico study

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Objective: Dipeptidyl peptidase IV (DPP-IV) is enzyme that degrades incretins to reduced abnormal visceral adipose tissue metabolism and insulin secretion. DPP-IV inhibitors increase the levels of GLP-1 and GIP leading beta-cell insulin secretion in the pancreas, reducing postprandial and fasting hyperglycemia, and improving blood glucose control without inducing hypoglycemia. Some evidence has shown natural compounds have therapeutic effects for human diseases. This study aimed to determine Indonesian phytochemicals virtually as DPP-IV inhibitors for type II diabetes mellitus (DM) therapy.

Methods: In silico study using molecular docking between DPP-IV (PDB : 5J3J), Sitagliptin, and Indonesian phytochemicals. The phytochemicals were obtained from HerbalDB and met the criteria for Lipinski's rule for drug availability. Macromolecule preparation was done using AutoDock, while the molecular docking process used PyRx. Protein-ligand interaction was visualized using Pymol. The indicators for data analysis were binding energy score must lower than Sitagliptin (-8.6 kcal/mol), root-mean-square deviation (RMSD) score $\leq$2 Å, and bound with DPP-1V residues where Sitagliptin bind, such as Glu`205, Glu206, Tyr662, and Arg358.

Results: The docking results showed that 1.10-Phenanthroline Monohydrate, Roxburghine B, and Lanuginosine had better potential activity to inhibit DPP-IV than Sitagliptin. 1.10-Phenanthroline Monohydrate, Roxburghine B, and Lanuginosine had lower binding scores (-8.7±0.1, -8.7±0.1, and -8.7±0.1 kcal/mol, respectively) than the standard ligand. In addition, they bound to DPP-IV at Glu`205, Glu206, Tyr662, and Arg358 residues. 1.10-Phenanthroline Monohydrate, Roxburghine B, and Lanuginosine are originally isolated from the seed of the plant Zea mays, the leaves and stems of the plant Uncaria gambir, and the leaves of the plant Annona mucirata, respectively.

Conclusion: New DPP-IV Inhibitor from Indonesian phytochemicals named 1.10-Phenanthroline Monohydrate, Roxburghine B, and Lanuginosine have been discovered as novel potential therapy for type II diabetes mellitus

PE132 Basic & translational diabetes research

Association between zinc-related genetic variants and risks of diabetes and other metabolic outcomes in Filipino adults

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Objective: We investigated in this pilot candidate gene studies the potential association between zinc-related single nucleotide polymorphisms (SNPs) and the risks of diabetes and other metabolic outcomes among Filipinos.

Methods: Using the most recent Philippine nutrition survey data, we first determined the SNPs associated with serum zinc concentration and zinc deficiency risk among ~800 adult respondents in the National Capital Region. Multivariate logistic regressions were performed to investigate the association of zinc-related SNPs with the risks of diabetes, dyslipidemia, hypertension, obesity, and central obesity following an additive genetic model of inheritance. Models were adjusted for sex, age and age-squared, smoking status, and physical activity levels as covariates.

Results: We initially identified 14 SNPs that showed significant variations in zinc levels across genotypes, 16 SNPs associated with serum zinc concentration, and 22 SNPs associated with zinc deficiency among study participants. Of these, 15 zincrelated SNPs further demonstrated association with the risks of metabolic disorders and various health indicators. We observed repeated associations as follows: *LINC02669/LOC105376360* rs2165468 with diabetes, dyslipidemia, and hypertension; *FKBP5* rs1360780 with diabetes, hypercholesterolemia, obesity, and central adiposity; *FKBP5* rs9470080 with abnormal lipid profile; *PPIG* rs13382615 with diabetes and hypertension; *PCSK1* rs6234 with low HDL-cholesterol and hypertension; *KNG1* rs10937266 with diabetes and obesity; *KNG1* rs11927941 with hypertriglyceridemia and obesity; *DIO2* rs225012 with hypertension and central adiposity, and; *TMPRSS6* rs1421312 with hypercholesterolemia and obesity.

Conclusion: Such findings provide initial evidence to support the roles of underlying genetic variants in the pathophysiology of diabetes and other chronic metabolic conditions, through altered zinc homeostasis, among Filipinos.

PE133 Basic & translational diabetes research

Consumption in the digital age: a mixed-methods study of diabetes mellitus risk factors in overweight thai children

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Objective: The prevalence of overweight and obesity among Thai children has increased, raising concerns about diabetes mellitus (DM) risk. Simultaneously, the digital era has profoundly influenced consumption behaviors, potentially affecting dietary choices and DM awareness. This study investigated the consumption behaviors of overweight children in the digital age, focusing on the impact of digital media exposure.

Methods: This research employed a cross-sectional mixed-methods approach. Quantitative surveys examined dietary habits, screen time, and types of digital media consumed. Qualitative semi-structured interviews explored perceptions of digital media influence and consumption behaviors.

Results: Quantitative data revealed that children who spend significant time (2.30-3.15 hours) on digital media, particularly those consuming short videos, were more likely to choose unhealthy food products and follow popular, often imbalanced, dietary trends. Additionally, a negative correlation was found between screen time and DM awareness. Qualitative analysis identified two key themes: Impact of Digital Media: Children are heavily exposed to digital advertisements promoting unhealthy foods, influencing their dietary choices. Excessive screen time contributes to sedentary behavior, further increasing DM risk. Social Influences: Peer pressure and social media trends drive children towards trendy, often unhealthy food choices, potentially leading to imbalanced nutrition and weight gain.

Conclusion: The findings underscore the significant influence of digital media on the consumption behaviors of overweight children, highlighting a heightened risk of DM. Excessive screen time, exposure to unhealthy food advertisements, and susceptibility to social media trends collectively contribute to poor dietary choices and reduced DM awareness. This research emphasizes the need for targeted interventions that address digital media's influence on children's health behaviors, promote healthy food choices, and raise awareness of DM risk factors in the digital age.

PE187 Clinical diabetes and therapeutics

Tirzepatide reduces HbA1c and body weight significantly more than placebo regardless of insulin sensitivity and beta cell function: post hoc analysis from SURMOUNT-2

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Objective: In the SURMOUNT (SM)-2 study, tirzepatide treatment led to substantial improvements in body weight (BW) and HbA1c compared to placebo in participants with obesity and type 2 diabetes. In this analysis, we assessed whether baseline markers of pancreatic beta cell function and insulin sensitivity were associated with the magnitudes of BW and glycemic reductions.

Methods: Post hoc analyses examined changes from baseline in BW and HbA1c in SM-2 at 72 weeks across HOMA2-B (computed with C-peptide) and HOMA2-IR (computed with insulin) quartiles (Q) from low (lower beta cell function/insulin resistance) (Q1) to high (Q4) as assessed by a mixed model for repeated measures using efficacy estimand.

Results: BW and HbA1c reductions were greater with tirzepatide 10 mg and 15 mg compared to placebo within each HOMA2-B and HOMA2-IR baseline Q. More participants across all Qs achieved ≥15% BW reduction with tirzepatide (36-63%) compared to placebo (up to 4%). More participants across all Qs reached HbA1c <5.7% with tirzepatide (ranging from 42-71%) compared to placebo (up to 6%).

Conclusion: Tirzepatide was more effective than placebo in reducing BW and HbA1c regardless of beta cell function and insulin resistance in participants with obesity and type 2 diabetes. BW reductions with tirzepatide trended greater with higher beta cell function, whereas HbA1c reduction trended greater with lower beta cell function.

PE188 Clinical diabetes and therapeutics

Unlocking therapeutic potential: Indonesian phytochemicals as PPAR-gamma activators for type II diabetes mellitus treatment

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Objective: Peroxisome proliferator-activated receptor γ (PPAR-γ) exhibits high expression in adipose tissue, overseeing adipogenesis, lipid metabolism, and insulin sensitivity. Its inhibition contributes to improved insulin sensitivity and enhanced glucose metabolism, acting as a pivotal regulator of adipogenesis by promoting the generation of small, insulin-sensitive adipocytes. The activation of PPAR-γ in mature adipocytes triggers the expression of various genes associated with enhanced insulin sensitivity. Some evidence has shown that natural compounds have therapeutic effects for some human diseases. Therefore, this study aimed to identify Indonesian phytochemicals virtually as PPAR-γ for type II diabetes mellitus (DM) therapy.

Methods: The research employed an in silico approach involving molecular docking among PPAR-γ (PDB: 2PRG), Rosiglitazone, and Indonesian phytochemicals. Phytochemicals sourced from HerbalDB met Lipinski's rule criteria for drug availability. Macromolecule preparation utilized AutoDock, while PyRx facilitated the molecular docking process. Protein-ligand interactions were visualized using Pymol. Data analysis relied on indicators, including a binding energy score lower than Rosiglitazone (-7.1 kcal/mol), a root-mean-square deviation (RMSD) score of ≤2 Å, and binding with PPAR-γ residues akin to those of Rosiglitazone, such as Ser289, His323, Tyr473, and Gln286.

Results: The docking results showed that Aegeline, Dihydroguaiaretic acid and Xanthyletin had better potential activity to activate PPAR-γ than Rosiglitazone. Aegeline, Dihydroguaiaretic acid, and Xanthyletin had lower binding scores (-8.0±0.1, -7.8±0.1, and -7.7±0.1 kcal/mol, respectively) than the standard ligand. In addition, they bound to PPAR-γ at Ser289, His323, Tyr473, and Gln286 residues. Aegeline, Dihydroguaiaretic acid, and Xanthyletin are originally isolated from the leaves of the plant Aegle marmelos, the seed of the plant Myristica Houtt, and the leaves of the plant Stauranthus perforates, respectively.

Conclusion: Novel potential therapies for type II diabetes mellitus have been identified in Indonesian phytochemicals, specifically Aegeline, Dihydroguaiaretic acid, and Xanthyletin, which act as newly discovered PPAR-γ activators.

PE189 Clinical diabetes and therapeutics

Identification of hinokinin, dihydroguaiaretic acid, and deoxylapachol as new GPR40 activators from Indonesian phytochemicals for treating type 2 diabetes mellitus through virtual screening

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Objective: GPR40 is a class A G-protein coupled receptor (GPCR) found in the pancreas, intestine, brain, and other tissues. GPR40 agonists can enhance insulin levels directly by stimulating the pancreatic beta cells and indirectly by the synergistic effect of elevated plasma levels of the incretin GLP-1. Some evidence has shown that natural compounds have therapeutic effects for some human diseases. Therefore, this study aimed to identify Indonesian phytochemicals virtually as GPR40 for type II diabetes mellitus (DM) therapy.

Methods: A computational investigation was conducted employing molecular docking techniques to analyze the interactions among GPR40 (PDB: 4PHU), TAK-875, and phytochemicals sourced from Indonesia. The phytochemicals were obtained from HerbalDB and met the criteria for Lipinski's rule for drug availability. Macromolecule preparation was done using AutoDock, while the molecular docking process used PyRx. Protein-ligand interaction was visualized using Pymol. The indicators for data analysis were binding energy score must lower than TAK-875 (-10,1 kcal/mol), Root-Mean-Square Deviation (RMSD) score ≤ 2 Å, and bound with GPR40 residues where TAK-875 bind, such as Tyr 91, Arg183, Ala83, Phe87, Gly139, Leu158, Phe142 and Arg2258.

Results: The docking results showed that Hinokinin, Dihydroguaiaretic acid and Deoxylapachol had better potential activity to activate GPR40 than TAK-875. Hinokinin, Dihydroguaiaretic acid, and Deoxylapachol had lower binding scores (-10.2±0.1 kcal/mol) than the standard ligand. In addition, they bound to GPR40 at Tyr 91, Arg183, Ala83, Phe87, Gly139, Leu158, Phe142 and Arg2258 residues. Hinokinin, derived from plants like Chamaecyparis and Zanthoxylum, exhibits antioxidant, anticancer, antiviral, and antitrypanosomal properties. Dihydroguaiaretic acid, sourced from the creosote bush, is a phenolic lignan with antioxidant, anti-inflammatory, and potential anticancer properties. Deoxylapachol is a cytotoxic component with antifungal and anticancer activities.

Conclusion: New GPR40 activators from Indonesian phytochemicals named Hinokinin, Dihydroguaiaretic acid, and Deoxylapachol have been discovered as novel potential therapies for type II DM.

PE190 Clinical diabetes and therapeutics

Challenges in managing steroid-induced diabetes among cancer patients: case series of experiences from National Referral Cancer Hospital

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Introduction: Elevated blood glucose (BG) could affect the effectiveness of chemotherapeutic agents, making steroid-induced hyperglycemia an entity that needs to be treated quickly. Here, we present three cases of steroid-induced diabetes mellitus (SIDM) in three cancer patients. These patients are all treated with a chemotherapy-steroid regimen.

Case Series: Case 1 A 53-year-old female with rectal adenocarcinoma originating from the ovarium. Evaluation after first cycle of chemotherapy, the patient's BG was elevated to 216 mg/dL, prompting treatment using basal insulin with correctional dose adapting to BG spikes, reducing the patient's blood glucose to 102 mg/dL and continuing to stabilize. Case 2 A 44-year-old female with breast cancer. On the third chemotherapy cycle, the patient's BG rose to 444 mg/dL. The patient's hyperglycemia was treated using an insulin sliding scale only, but BG remained elevated. After two years of loss follow-up. The patient came with a BG of 385 mg/dL, treatment was then switched to using basal insulin. Yearly evaluation came with a random BG value of 387 mg/dL. Our team then decided to combine the basal insulin treatment with gliclazide 60 mg once daily and metformin 500 mg thrice daily. The patient's current diagnosis was changed to type 2 diabetes. Case 3 A 67-year-old male with lung carcinoma. During the second chemotherapy cycle evaluation, the patient's BG spiked to 386 mg/dL. The patient was then given insulin basal and gliclazide once daily. Two weeks later, the patient's BG has been successfully reduced to 226 mg/dL. We then add insulin prandial to the treatment. Using basal insulin + gliclazide + prandial insulin, the patient's blood glucose has been reduced to 188 mg/dL.

Conclusions: SIDM in cancer patients is intertwined with pharmacological impact of glucocorticoids on glucose metabolism. It is a great challenge for us to prevent that from becoming Type 2 Diabetes

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PE016 Basic & translational diabetes research

Harnessing Indonesian biodiversity: in silico discovery of novel PPAR-gamma agonists from miraxanthin-V, marmesin, and cryptolepine for type II diabetes mellitus treatment

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Objective: Type II diabetes mellitus (T2DM) remains a global health crisis, with Indonesia facing rising prevalence linked to metabolic dysregulation. Peroxisome proliferator-activated receptor γ (PPAR-γ) activation enhances insulin sensitivity and glucose metabolism by regulating adipogenesis and lipid homeostasis. Synthetic PPAR-γ agonists like Rosiglitazone exhibit adverse effects, necessitating safer alternatives. Indonesia's biodiversity, documented in phytochemical databases, offers unexplored sources for novel PPAR-γ modulators with improved safety profiles.

Methods: Computational screening targeted PPAR-γ (PDB:2PRG) using molecular docking. Three Indonesian phytochemicals—*Miraxanthin-V*, *Marmesin*, and *Cryptolepine*—were selected from HerbalDB, filtered via Lipinski's Rule of Five. Macromolecule preparation in AutoDock Tools included water removal, polar hydrogen addition, and Kollman charge assignment. Docking simulations used PyRx 0.8 with AutoDock Vina. Protein-ligand interactions were analyzed in PyMOL 2.5.2, focusing on residues Ser289, His323, Tyr473, and Gln286. Compounds were evaluated against Rosiglitazone (-7.1 kcal/mol) using: (1) binding energy ≤-7.1 kcal/mol; (2) RMSD ≤2 Å; (3) interaction with ≥2 key residues.

Results: Three Indonesian phytochemicals demonstrated superior PPAR-γ binding: 1) Miraxanthin-V (PubChem CID 135438594; binding affinity: -7.7 kcal/mol) from Mirabilis jalapa; 2) Marmesin (CID 334704; -7.7 kcal/mol) isolated from Aegle marmelos; and 3) Cryptolepine (CID 82143; -7.6 kcal/mol) sourced from Indonesian alkaloid-bearing plants. All compounds exceeded Rosiglitazone's binding affinity (-7.1 kcal/mol) and exhibited stable RMSD values (≤2 Å). Each interacted with ≥3 key PPAR-γ residues (Ser289, His323, Tyr473, Gln286), confirming robust molecular compatibility.

Conclusion: *Miraxanthin-V*, *Marmesin*, and *Cryptolepine* demonstrated enhanced PPAR-γ binding affinities compared to Rosiglitazone. As natural PPAR-γ agonists, they offer promising therapeutic potential for T2DM with potentially reduced side effects. Future studies should validate these findings through in vitro PPAR-γ activation assays and in vivo models to assess efficacy in glucose homeostasis and insulin sensitization.

PE017 Basic & translational diabetes research

Fabrication and characterization of stabilized biogenic silver nanoparticles with rifabutin: evaluation of antidiabetic activity in streptozotocin-induced diabetic albino wistar rats

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Objective: Diabetes mellitus (DM) and its complications are a severe public health concern due to the high incidence, morbidity, and mortality rates. The present study accounts for an expeditious technique for the synthesis of silver nanoparticles (AgNPs) utilizing rifabutin that involved in the reduction and capping of AgNPs and leads to the formation of stable biogenic Rifabutin-AgNPs.

Methods: The morphology of Rifabutin -AgNPs were optimized using various analytical tools such as UV-visible, FT-IR and X-ray diffraction (XRD), FESEM-EDS and Transmission electron microscopy (TEM) analysis confirmed that the Rifabutin -AgNPs have reasonably good stability. Furthermore, the synthesis of Rifabutin-AgNPs were successfully employed to examine them *in vivo* antidiabetic potential against streptozotocin-induced albino wistar rats compared to standalone rifabutin and standard drug metformin group. The Rifabutin-AgNPs at a dose of 5 mg/kg and 10 mg/kg along with only rifabutin at a dose of 50 mg/kg and 100 mg/kg and metformin 5 mg/kg were administrated daily to diabetic induced rats for 14 days and explored blood glucose level, body weight variation, insulin level, total lipid profile, liver function and histopathological studies of the pancreas and liver.

Results: Throughout study, it was observed that diabetic rats treated with synthesized rifabutin-AgNPs and demonstrated significant reduction in fasting blood glucose level, insulin level, lipid profile also preventing subsequent weight loss compared to untreated diabetic groups. The photomicrograph of histopathological revealed the significant regeneration of impaired pancreatic and liver cells compared to untreated diabetic rats. However, rifabutin standalone exhibited promising outcome. Therefore, study concluded that Rifabutin synthesized AgNPs has antidiabetic potential biogenic nano-formulated agents to hinder the progression of diabetes.

Conclusion: Rifabutin-mediated biosynthesis of silver nanoparticles presents a promising, stable biogenic nanoformulation with significant antidiabetic potential. Rifabutin-AgNPs demonstrated superior therapeutic efficacy in ameliorating diabetes-induced biochemical and histological alterations, indicating their potential as effective antidiabetic agents.

PE018 Basic & translational diabetes research

Non-exercise activity thermogenesis (NEAT) and insulin resistance: a narrative review of evidence and mechanisms

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Objective: Insulin resistance (IR) is a key characteristic of metabolic syndrome and serves as a precursor to type 2 diabetes mellitus (T2DM). While structured exercise is known to improve insulin sensitivity, there has been growing interest in the role of non-exercise activity thermogenesis (NEAT), which refers to the energy expended on daily activities aside from intentional exercise. This narrative review aims to synthesize current evidence regarding the contributions of NEAT in reducing insulin resistance, explore its physiological mechanisms, and highlight its implications for public health interventions.

Methods: A literature review was conducted using databases such as PubMed, Scopus, and Web of Science. The review included observational studies, interventional trials, and mechanistic investigations published between 2000 and 2024. Key search terms used were "NEAT," "non-exercise activity thermogenesis," "insulin resistance," and "sedentary behavior."

Results: The findings consistently indicate that increased NEAT is associated with improved insulin sensitivity, independent of structured exercise. Interrupting sedentary periods with light physical activity enhances cellular glucose uptake, may modulate adipokines, and reduces markers of inflammation. Intervention studies have demonstrated that even modest increases in NEAT can result in substantial reductions in glycemic markers.

Conclusion: NEAT represents a viable, low-barrier behavioral target for reducing insulin resistance. Public health strategies that promote light-intensity daily activities, such as standing, taking walking breaks, and engaging in household chores, may lead to sustainable improvements in metabolic health, especially among sedentary individuals.

PE019 Basic & translational diabetes research

Causal effects and pathways of dietary intake on type 2 diabetes and diabetic complications: a comprehensive mendelian randomization study

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Objective: Type 2 diabetes and its complications impose a significant burden on both individuals and society. While observational studies, systematic reviews, and meta-analyses indicate that dietary interventions play a critical role in the prevention and management of type 2 diabetes, there is limited detailed research on the causal effects of specific diets and their underlying mechanisms. This study aimed to investigate the causal effects of 119 dietary factors on type 2 diabetes and its complications, focusing on the mediating roles of metabolic markers, plasma proteins, metabolites, and gut microbiota.

Methods: A Mendelian randomization approach was applied to examine the causal relationships between dietary factors and the risk of type 2 diabetes and its complications. Metabolic markers such as triglycerides, glycated hemoglobin (HbA1c), high-density lipoprotein cholesterol (HDL-C), and apolipoprotein A were assessed, alongside plasma proteins, metabolites, and gut microbiota.

Results: Alcohol intake frequency was identified as a risk factor for type 2 diabetes (odds ratio [OR] 1.346, 95% confidence interval [CI] 1.142-1.587, adjusted P=0.046), potentially increasing triglycerides, HbA1c, and the plasma protein SPATA31D4, while reducing HDL-C, apolipoprotein A, and the metabolite 1-palmitoleoyl-sn-glycero-3-phosphocholine. Conversely, cheese intake appeared to have a protective effect against type 2 diabetes (OR 0.608, 95% CI 0.470-0.787, adjusted P=0.024), diabetic maculopathy (OR 0.502, 95% CI 0.302-0.835, P=0.008), and retinopathy (OR 0.547, 95% CI 0.375-0.799, P=0.002) by lowering triglycerides, fasting insulin, and HbA1c, and increasing HDL-C and apolipoprotein A.

Conclusion: This Mendelian randomization study provides genetic evidence for the causal effects of specific dietary factors on type 2 diabetes and its complications, identifying alcohol as a risk factor while suggesting a protective role for cheese. These findings offer valuable insights into the underlying biological mechanisms, including the involvement of plasma proteins and metabolic markers.

PE287 Diabetes complications-basic & translational

Indonesian medicinal plant-derived withanolide D, thwaitesixanthone, and xylopine as novel DPP-IV inhibitors for diabetes-associated osteoarthritis

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Objective: Diabetes-associated osteoarthritis (OA) is exacerbated by obesity-driven metabolic dysfunction and chronic inflammation. This study investigated Indonesian medicinal plant-derived compounds for dipeptidyl peptidase IV (DPP-IV) inhibition, a therapeutic target linking glucose metabolism and joint degeneration.

Methods: A computational screening of 517 Indonesian phytochemicals from HerbalDB, preselected via Lipinski's rule of five for drug-likeness, was conducted against the DPP-IV enzyme (PDB:5J3J). The macromolecule was prepared using AutoDock Tools 1.5.6, involving water molecule removal, polar hydrogen addition, and Kollman charge assignment. Molecular docking simulations were executed in PyRx 0.8 with AutoDock Vina, employing an exhaustiveness parameter of 8 to generate 10 binding conformations per ligand. Protein-ligand interaction profiling was performed in PyMOL 2.5.2, focusing on residues Glu205, Glu206, Tyr662, and Arg358. Compounds were prioritized based on three criteria: (1) binding energy ≤−8.6 kcal/mol (reference: Sitagliptin), (2) root-mean-square deviation (RMSD) ≤2 Å relative to the crystallographic ligand, and (3) formation of stable interactions with ≥2 catalytic residues.

Results: Three Indonesian phytochemicals demonstrated superior DPP-IV inhibition: 1) Withanolide D (PubChem CID 301754; binding affinity: −9.2 kcal/mol) isolated from *Withania somnifera* (Ashwagandha), cultivated in Indonesian traditional medicine systems; 2) Thwaitesixanthone (PubChem CID 392169; binding affinity: −9.2 kcal/mol) sourced from *Garcinia thwaitesii*, a native Indonesian plant of the Clusiaceae family; and 3) Xylopine (PubChem CID 160503; binding affinity: −9.0 kcal/mol) identified in *Xylopia parviflora*, a medicinal plant endemic to Indonesian forests. All compounds exhibited binding affinities surpassing Sitagliptin (−8.6 kcal/mol) and stable RMSD values (0.0 Å), indicating robust molecular interactions. Their structural diversity and origin in Indonesian flora highlight potential dual mechanisms in modulating DPP-IV activity and mitigating metabolic-inflammatory crosstalk in diabetic OA.

Conclusion: Withanolide D, Thwaitesixanthone, and Xylopine are potent DPP-IV inhibitors derived from Indonesian medicinal plants, offering novel therapeutic candidates for diabetes-associated OA. Further studies should validate their efficacy in glucose metabolism regulation and cartilage protection.

PE288 Diabetes complications-basic & translational

Endothelial ferroptosis as a causal driver of diabetic nephropathy: insights from multi-omics and mendelian randomization

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Objective: Diabetic nephropathy (DN) has emerged as a predominant contributor to end-stage renal disease globally. Recent studies have highlighted ferroptosis as a potentially critical factor in DN pathogenesis. Despite growing evidence linking ferroptosis to DN progression, the causal mechanisms remain poorly understood. Moreover, the precise involvement of ferroptosis-related genes in glomerular cell dysfunction during DN development warrants further investigation.

Methods: We first retrieved 933 ferroptosis-related genes from the FerrDb database. Using cis-expression quantitative trait loci data from the eQTLGen consortium, we performed Mendelian randomization to assess the causal effects of these genes on type 2 diabetes. Genes demonstrating significant associations were further evaluated for their causal roles in DN. To ensure robustness, we validated key candidate genes using independent datasets from multiple sources. Finally, we integrated single-cell RNA sequencing (scRNA-seq) and single-cell ATAC sequencing (scATAC-seq) data from DN kidney tissues to explore cell-type-specific expression patterns, differential expression across glomerular cell subtypes, and potential transcriptional regulators of these genes.

Results: *CDKN1A* was identified as a potential risk factor for DN, whereas *CEBPG* and *EPAS1* exhibited protective effects. Multi-omics integration demonstrated pronounced activation of ferroptosis signaling in endothelial cells, which was closely linked to inflammatory cell infiltration. *CDKN1A*, *CEBPG*, and *EPAS1* were predominantly enriched in endothelial cells and displayed elevated chromatin accessibility. *FOS*, *FOSL2*, and *BHLHE40* may serve as upstream regulators of *CDKN1A*, potentially governing its expression and downstream pathological effects.

Conclusion: *CDKN1A*, *CEBPG* and *EPAS1* were identified as key regulators of endothelial ferroptosis in DN, highlighting their potential as molecular targets for intervention.

PE289 Diabetes complications-basic & translational

Stem cell therapy for the treatment of diabetic complications: a systematic review of clinical evidence

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Objective: Diabetes mellitus (DM) is a chronic condition often leading to debilitating complications such as neuropathy, nephropathy, and vascular diseases, which significantly impair patients' quality of life and place a heavy burden on healthcare systems. While conventional treatments can manage symptoms, they often fail to reverse tissue damage or halt disease progression. Stem cell therapies, particularly those involving mesenchymal stromal cells (MSCs), have emerged as a promising alternative. This review evaluates the clinical efficacy and safety of MSC-based therapies for managing both type 1 and type 2 diabetes-related complications.

Methods: A thorough literature search was conducted in PubMed, Scopus, and EBSCO databases up to May 2025. Clinical trials involving human participants using MSCs or their derivatives to treat DM-related complications were included. Data on clinical outcomes, safety profiles, recurrence rates, and long-term follow-up were systematically collected and analyzed.

Results: Eight studies met the inclusion criteria. In type 1 DM, co-transplantation of umbilical cord MSCs with autologous bone marrow mononuclear cells resulted in significant improvements in neuropathy and nephropathy over an 8-year period. For type 2 DM, therapy using bone marrow-derived MSCs and mononuclear cells similarly reduced long-term vascular complications. MSCs from umbilical cord, bone marrow, and placenta, along with their secretomes, have shown remarkable potential in promoting tissue repair, enhancing angiogenesis, and regulating inflammation. Hypoxia-conditioned MSCs and secretome gels further demonstrated significant anti-inflammatory effects. No serious adverse events, including tumor formation, were reported in any of the studies.

Conclusion: MSC-based therapies, whether cell-based or cell-free, demonstrate substantial promise in mitigating diabetes related complications and improving patient outcomes with a favorable safety profile. However, additional large-scale multicenter trials are needed to refine treatment protocols, optimize dosing, and confirm long-term therapeutic benefits.

PE290 Diabetes complications-basic & translational

Loss of MsrB2 accelerates hypertension cardiac fibrosis in diabetes

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Objective: This study aimed to elucidate the role of methionine sulfoxide reductase B2 (MsrB2) in cardiac remodeling under diabetic and hypertensive conditions, particularly in the context of lean diabetes.

Methods: We analyzed blood pressure and glucose tolerance in diabetic mouse models, comparing lean and obese phenotypes, and assessed MsrB2 expression in both mouse and human cardiac tissue. To investigate the functional role of MsrB2 in cardiac remodeling, vascular stress was induced via angiotensin II (AngII) infusion in MsrB2 knockout (KO) mice. Myocardial fibrosis, extracellular matrix (ECM) deposition, structural integrity, and contractile function were evaluated through histological, molecular, and transcriptomic analyses. Additionally, the therapeutic potential of MsrB2 was examined by cardiomyocyte-specific overexpression in the presence of vascular stress.

Results: Elevated blood pressure was observed in diabetic mice irrespective of BMI; however, glucose intolerance was significantly more pronounced and MsrB2 expression markedly reduced in lean diabetic mice compared to obese counterparts. Human heart tissue affected by high blood pressure similarly exhibited reduced MsrB2 expression. In response to AngII-induced vascular stress, MsrB2 KO mice demonstrated significantly enhanced myocardial fibrosis, ECM accumulation, and structural disorganization compared to wild-type controls. Transcriptomic profiling revealed upregulation of fibrosis-related ECM and collagen pathways. MsrB2 deficiency was also associated with impaired cardiac contractility, reduced SERCA2a expression, and disrupted sarcomere Z-lines. Conversely, MsrB2 overexpression reversed fibrotic remodeling, restored SERCA2a levels, and preserved myocardial structure.

Conclusion: MsrB2 plays a critical role in regulating cardiac remodeling under hypertensive conditions in diabetes. Its reduced expression in lean diabetes and hypertensive human hearts suggests heightened susceptibility to vascular stress. Therapeutic modulation of MsrB2 may offer a novel strategy for preventing or treating cardiac fibrosis and dysfunction in metabolic heart disease.