Aim: This study aimed to compare the exosomal miRNA profiles between clinically diagnosed T2D patients as compared to non-T2D controls (HbA1c< 6.3 %). Secondly, it also evaluated the changes in exosomal miRNA profiles in T2D patients after a 24-week intervention with UKMRC9.

Method: Plasma exosomes were isolated from 72 Rice Intervention in Chronic Healthy (RICH) participants and characterized using transmission electron microscopy (TEM), nanoparticle tracking analysis (NTA), and western blotting. Total RNAs from exosomes were extracted to construct miRNA libraries for next-generation sequencing (NGS). Lastly, the Gene Ontology (GO) and Kyoto Encyclopaedia Genes and Genomes (KEGG) analyses were conducted to predict the downstream targets of the dysregulated genes.

Results: TEM and NTA analyses revealed no significant differences in exosome size and concentration between T2D patients and non-T2D controls. However, the bioinformatics analyses of NGS data identified 12 differentially expressed exosomal miRNAs in T2D patients as compared to non-T2D controls, with 6 miRNAs upregulated and 6 downregulated (log fold change >1, FDR $p < 0.05$). After the UKMRC9 intervention, a subset of exosomal miRNAs in T2D patients returned to levels similar to non-T2D controls. GO and KEGG pathway analyses linked these exosomal miRNAs to several T2D-related pathways.

Conclusion: Consumption of UKMRC9 altered the exosomal miRNA profiles in T2D patients to levels similar to non-T2D controls. Thus, UKMRC9 could serve as an alternative approach to manage, and potentially reverse T2D.

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IL-6 knockout mice nutri-stressed with high-fat diet show improved glucose tolerance and insulin resistance

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Background: Interleukin-6 (IL-6) is a major cytokine that plays a role in inflammation and metabolism. Its role in adipose tissue, as well as in obesity-induced impairment in glucose homeostasis and insulin resistance, remains elusive.

Aim: We aimed to investigate the effect of a global knockout of IL-6 (IL-6 $^{-/-}$) on glucose homeostasis in mice fed with high-fat diets.

Method: C57BL/6 male mice (n = 20) and IL-6 $^{-/-}$ male mice (n = 20) were randomly assigned to two dietary interventions, including Chow (n=10) or HFD (n = 10), for 22 weeks. Intraperitoneal glucose tolerance tests (IP-GTT) and intraperitoneal insulin tolerance tests (IP-ITT) were performed. Blood samples were collected for metabolic hormone measurements.

Results: IL-6 $^{-/-}$ mice fed with a high-fat diet showed significantly ($P > 0.0001$) lower fasting blood glucose concentrations (6.3 ± 0.2 mmol.L^{-1}) than wild-type mice fed on the same high-fat diet (8.9 ± 0.4 mmol.L^{-1}). During IP-GTT and IP-ITT, IL-6 $^{-/-}$ mice fed with a high-fat diet showed significantly ($P = 0.007$ and $P > 0.0001$, respectively) lower area-under-the-curve (AUC: 1610 ± 140 and 493 ± 62.2, respectively) than wild-type mice fed on the same high-fat diet (2203 ± 120 and 956 ± 45, respectively). IL-6 $^{-/-}$ mice fed a high-fat diet showed significantly ($P = 0.037$ and $P = 0.045$, respectively) lower serum leptin and MCP-1 concentrations (9820 ± 1174 and 322 ± 113 pg.mL^{-1}, respectively) than wild-type mice fed the same high-fat diet (13196 ± 940 and 344 ± 99 pg.mL^{-1}, respectively). Fasting insulin concentrations were significantly ($P = 0.027$) higher in IL-6 $^{-/-}$ mice fed with a high-fat diet (8427 ± 746 pg.mL^{-1}) than in wild-type mice fed the same high-fat diet (6349 ± 438 pg.mL^{-1}).

Conclusion: Our findings suggest that a global knockout of the IL-6 might improve insulin resistance and glucose intolerance in mice nutri-stressed with a high-fat diet.

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Global and mitochondrial epigenetic profiles in type 2 diabetes: Findings from the RICH study

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Background: With more than 500 million adults afflicted with type 2 diabetes (T2D) globally, studies have shown that T2D could be managed with lifestyle and dietary interventions [1,2]. The inherent plasticity of epigenetics presents another perspective on the development, progression and management of T2D [3]. While numerous studies link epigenetic changes to improved outcomes in T2D patients, the epigenetic profile of T2D patients in Asian populations is not fully elucidated.

Aim: To compare the epigenetic profile of T2D patients and healthy controls and to evaluate changes in the epigenetic profile in T2D patients after a 24-week intervention with low glycaemic index red rice (UKMRC9).

Method: DNA was extracted from peripheral blood mononuclear cells (PBMC) isolated from 96 participants in the Rice Intervention in Chronic Healthy (RICH) study and used for global DNA methylation level analysis. In addition, targeted bisulphite sequencing (BS-seq) of mitochondrial DNA (mtDNA) and four selected nuclear DNA (nDNA) genes was also carried out.

Results: T2D patients had significantly lower global DNA methylation levels in PBMC than healthy controls (0.84 % ± 0.04 and 1.32 % ± 0.12 respectively, $p < 0.01$). After 24 weeks of UKMRC9 intervention, the global DNA methylation levels increased to 1.13 % ± 0.02 ($p < 0.01$) in T2D patients. Targeted BS-seq analyses identified 11 differentially methylated regions (DMRs) in the mtDNA of T2D patients compared to the healthy controls (absolute-log fold change >1 and FDR <0.05). No DMRs were observed in the mtDNA of T2D patients post-UKMRC9. In nDNA, DMRs were identified in three appetite-regulating genes - ghrelin, cholecystokinin and leptin - in T2D patients compared to healthy controls. Significant DMRs were also observed in these genes of T2D patients post-UKMRC9 intervention.

Conclusion: UKMRC9 intervention altered the global epigenetic profiles of T2D patients, making them more comparable to those of healthy controls. This suggest that epigenetic changes could serve as a surrogate measure to assess the effectiveness of interventions for T2D.

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Structural Modeling of Krüppel-like factor 15 zinc finger binding domain to DNA : Potential therapeutic target for T2D

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Background: Krüppel-like factor 15 (KLF15) is a transcription factor contributing to the pathophysiology of multiple diseases, including metabolic syndromes. It is 416 residues long, with a C2H2-type zinc finger (ZnF) domain that binds to GC-rich areas regulating transcription.

Aim: The role of KLF15 in glucogenesis and glucose level maintenance is well established. However, the DNA interaction mechanism at the atomic level remains unresolved.

Method: Here, we utilized computational biology tools to address this knowledge gap. The KLF15 ZnF–domain was modeled with AlphaFold 2.0 and docked with DNA. Alanine substitution of the KLF15 ZnF domain–DNA complex residues K334A, R334A, Y332A, and R392A significantly affected binding affinities (DDG) to DNA. To understand the conformational stability and dynamics of the KLF15 ZnF–domain complexes,100-ns molecular dynamics simulations were performed. Additionally, molecular mechanics-generalized Born surface area was utilized to calculate the total binding energies.

Results: The binding energies of the wild-type KLF15 ZnF domain (–83.5 ± 0.43 kcal/mol) demonstrated a more robust binding affinity to DNA than K334A (–44.50 ± 0.71 kcal/mol), R344A (−58.74 ± 0.61 kcal/mol), Y332A (−67.43 ± 0.43 kcal/mol), and R392A (−68.44 ± 0.56 kcal/mol).

Conclusion: In conclusion, the four identified residues are essential to recognize and bind DNA and can be a target to develop compounds for type 2 diabetes treatment.

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Insights into insulin clearance and disease progression: role of circulating CEACAM1 in the portuguese PREVADIAB2 study

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Background: Type 2 diabetes is a multifactorial condition, with its greatest impact from complications. We hypothesize that distinct insulin mechanisms, particularly insulin clearance, usually overlooked, and hepatic steatosis, can identify a phenotype at higher risk for complications (1, 2). Importantly, CEACAM1 in hepatocytes has been identified as a crucial regulator of hepatic insulin clearance and hepatic steatosis (2).

Aim: Herein, we hypothesize that circulating CEACAM1 reflects compromised insulin metabolism and hepatic steatosis identifying the phenotype at higher risk.

Method: A total of 1019 individuals from the PREVADIAB2 cohort were evaluated for diabetes and classified per WHO 2019