Commentary

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Journal of Clinical and Experimental Nephrology
ISSN 2472-5056

2024
Vol.9 No. 6:285

Hepatic Insulin Resistance in Type 2 Diabetes: Mechanisms and Therapeutic Insights

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Received date: November 22, 2024, Manuscript No. IPJCEN-24-19994; **Editor assigned date**: November 26, 2024, PreQC No. IPJCEN-24-19994 (PQ); **Reviewed date**: December 09, 2024, QC No. IPJCEN-24-19994; **Revised date**: December 16, 2024, Manuscript No. IPJCEN-24-19994 (R); **Published date:** December 23, 2024, DOI: 10.36648/2472-5056.9.6.285

Citation: Noah L (2024) Hepatic Insulin Resistance in Type 2 Diabetes: Mechanisms and Therapeutic Insights. J Clin Exp Nephrol Vol.9 No.6: 285.

Description

Type 2 Diabetes Mellitus (T2DM) is a long-lasting metabolic condition characterized by ongoing hyperglycemia resulting from insulin resistance and deficient insulin secretion. In addition to its systemic consequences, T2DM makes individuals vulnerable to liver-related issues, such as Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD). The interaction of disturbed insulin signaling, inflammation, oxidative stress and ectopic fat accumulation in the liver creates a complicated network of pathophysiology that aggravates the progression of the disease and complications. This review explores the mechanisms that underlie hepatic insulin resistance and the therapeutic possibilities offered by bioactive compounds, especially flavonoids. In normal hepatocytes, insulin attaches to its receptor, triggering a signaling cascade that Activates Protein Kinase B (Akt). Akt manages glucose uptake and energy metabolism, thus ensuring metabolic equilibrium. However, in T2DM, insulin resistance hinders this pathway, decreasing Akt phosphorylation and resulting in hyperglycemia. Chronic low-grade inflammation, referred to as meta-inflammation, is a defining feature of T2DM. Excessive generation of reactive pro-oxidant species results in oxidative stress, which disrupts insulin signaling by lowering tyrosine phosphorylation in insulin receptor substrates and Akt. Oxidative stress additionally activates Nuclear factor-κB (NF-κB), creating a destructive cycle of inflammation and insulin resistance.

Role of prostaglandins

Prostaglandin E2 (PGE2) emerges as a significant inflammatory mediator in T2DM. Produced via cyclooxygenase enzymes (COX-1 and COX-2), PGE2 production is elevated in hyperglycemic and inflammatory conditions. While raised serum PGE2 levels in T2DM emphasize its potential as a biomarker, its role in hepatic insulin resistance and lipid metabolism remains debated. Additional research is needed to clarify the COX-2-PGE2 pathway's role in metabolic dysfunction.

Flavonoids: Promising Therapeutic Agents lavonoids, a varied group of plant-derived polyphenols, show antioxidant, anti-inflammatory and antidiabetic effects, making them appealing options for addressing hepatic insulin resistance.

Antioxidant effects: Flavonoids counteract reactive species, alleviating oxidative stress and safeguarding cellular structures.

Anti-in lammatory properties: By influencing NF-κB and cytokine production, flavonoids lessen inflammation.

Glucose regulation: Flavonoids improve insulin sensitivity and glucose uptake by acting on signaling pathways such as Akt.

Challenges in therapeutic application

Notwithstanding their promise, flavonoids encounter challenges related to bioavailability and metabolism. When consumed orally, flavonoids are inadequately absorbed in the small intestine, with notable portions passing to the large intestine for excretion. Metabolites found in tissues and blood frequently differ from the original compounds, necessitating approaches to enhance their bioavailability.

Future directions: Encapsulation methods and nanoparticle-based delivery systems may enhance the stability and absorption of flavonoids.

Structural modifications: Chemical alterations to flavonoid structures could improve bioactivity and metabolic stability.

Clinical trials: Comprehensive clinical research is essential to verify efficacy and safety in treating T2DM-related hepatic insulin resistance.

Therapeutic implications: Addressing hepatic insulin resistance in T2DM necessitates a comprehensive strategy that focuses on inflammation, oxidative stress and impaired signaling. Flavonoids present potential as supplementary treatments because of their multifunctional actions. Merging flavonoid supplementation with changes in lifestyle and pharmacological treatments might offer a holistic approach to alleviate T2DM complications.

Conclusion

Hepatic insulin resistance is situated at the center of T2DM pathophysiology, fueled by inflammation, oxidative stress and impaired insulin signaling. Although there are ongoing therapeutic challenges, investigating bioactive compounds such

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as flavonoids uncovers new possibilities for intervention. A more profound comprehension of their mechanisms, alongside progress in delivery technologies, could lead to groundbreaking treatments that tackle both metabolic dysfunction and its broad-ranging effects.