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**PATHOPHYSIOLOGICAL ASPECTS OF DIABETES MELLITUS AND
MECHANISMS OF INSULIN RESISTANCE**
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Diabetes mellitus (DM) is a group of metabolic disorders characterized by chronic hyperglycemia due to impaired insulin secretion, action, or both. The global burden of type 2 diabetes mellitus (T2DM), driven largely by insulin resistance (IR), is rising sharply. IR, a key pathological feature of T2DM, involves reduced responsiveness of skeletal muscle, liver, and adipose tissues to insulin, resulting in impaired glucose uptake and increased hepatic glucose production.

Objective was to explore the molecular and physiological mechanisms contributing to insulin resistance in T2DM and their roles in disease progression.

Materials and methods includes a systematic review of recent peer-reviewed literature was conducted, focusing on insulin signaling, inflammatory mediators, oxidative stress, lipotoxicity, and cellular dysfunction in T2DM.

Impaired Insulin Signaling: In healthy states, insulin activates a cascade via IRS, PI3K, and AKT to promote GLUT4-mediated glucose uptake. In IR, serine phosphorylation of IRS disrupts downstream signaling, reducing PI3K/AKT activation and GLUT4 translocation. Additionally, hepatic IR enhances gluconeogenesis, worsening hyperglycemia.

Chronic Inflammation: Adipose tissue in obesity secretes pro-inflammatory cytokines like TNF-α and IL-6, which impair insulin signaling by modifying IRS proteins and suppressing their expression, contributing to systemic insulin resistance.

Lipotoxicity and FFAs (Free fatty acids): Elevated FFAs inhibit insulin signaling, promote ROS (reactive oxygen species) generation, and cause ectopic lipid accumulation (DAG, ceramides), which further disrupt glucose metabolism and insulin responsiveness.

Oxidative stress and mitochondrial dysfunction: excess ROS damage insulin receptors and impair vascular function through nitric oxide imbalance. Mitochondrial dysfunction reduces ATP production, weakening insulin-mediated metabolic processes.

ER stress: Accumulation of misfolded proteins in the ER activates the unfolded protein response (UPR), inhibiting IRS function and promoting inflammatory pathways. Chronic ER stress also leads to β-cell apoptosis, reducing insulin secretion.

Genetic and molecular defects: mutations or altered expression insulin receptors, IRS proteins, AKT, or PEARY impair signaling. Epigenetic changes also modulate insulin sensitivity.

Thus, insulin resistance arises from interrelated disruptions in insulin signaling, inflammation, lipid metabolism, oxidative stress, ER function and genetic or molecular defects. Targeted interventions such as PI3K/AKT pathway activators, anti-inflammatory agents, lipid-lowering strategies, and antioxidants–are essential AKT for improving insulin sensitivity and slowing T2DM progression.