#0060
Pathophysiology of Insulin Resistance: Connecting the Dots

Author(S):
Suresh N. Shinde,MD.

Organization/Affiliation:
Academy of Continuing Medical Education & research, Pune,India; Poona Hospital & Research Centre, Pune, India

Abstract
This hypothesis delineates the development of insulin resistance (IR) through basal, fasting, and prandial metabolic phases, elucidating a potential mechanism for Type 2 Diabetes (T2D) onset.

Basal Metabolism:
Myocytes create energy via TCA cycle using AcetylCoA derived from glucose (glycolysis) and fatty acids (beta-oxidation) via entry ports, which are controlled by insulin via GLP-1 and GIP(1-30), secreted by alpha cells.

Fasting Metabolism:
Pancreatic GLP-1/insulin and glucagon flip-flop cycle and adipose tissue GIP(1-30)/insulin and FGF21 flip-flop cycle alternately feed glucose and fatty acids to muscles. Muscle ‘true’ IR is generated as muscle glycogen accumulates closing glucose entry. Subsequent deficiency of G6P in liver activates FOXO-1, PPAR-alpha and FGF21, opens muscle FFA gate switching over to adipose tissue FGF21, GIP(1-30)/insulin flip-flop.

Prandial Metabolism:
In prandial metabolism, dietary fats trigger GIP(1-42)/insulin secretion, stimulating PPAR-gamma to generate exogenous subcutaneous fat and adiponectin (GIP1-42 incritinogauge). Conversely, dietary carbohydrates stimulate GLP-1/insulin secretion, closing the fatty acid entry in muscles and promoting glycogen synthesis. Excess glucose drives de-novo-lipogenesis, endogenous fat accumulation, and leptin (GLP-1 incritinogauge) secretion. The leptin/insulin isn't proportionate to glucose levels, leading to a fallacious ‘mathematical IR’ value, which does not represent ‘true IR’.

Leptin inhibits PPAR-gamma by phosphorylating at serine-273 residue, suppressing adiponectin and GIP42/insulin, causing lipolysis in exogenous fat, increasing fatty acid flux. This flux increase intra-myocytic beta-oxidation, and glycogen/triglyceride accumulation, but only triglyceride accumulation in liver, thus escalating universal true IR, hepatic glucose output, and hyper-FFAmia.

Eventually, saturated liver triglycerides and peripheral tissue glycogen halt de-novo-lipogenesis and leptin generation, triggering ghrelin levels to rise, promoting endogenous fat lipolysis, and suppressing leptin/GLP-1/insulin, contributing to T2D evolution.