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Insulin Resistance, Obesity and Polycystic Ovarian Syndrome in Diabetic Patients

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Editorial

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Metabolic Mechanisms of Insulin Resistance

Ingestion of diets with high fats or lipids is associated with obesity and increased storage of triglycerides at sites other than adipose tissue, including skeletal muscle, liver, the heart, and kidney. These changes cause chronic elevations in circulating free fatty acids and triacylglycerols (TAG). Extensive research has shown that adipose tissue is an important endocrine organ. Adipose cells produce a variety of hormones and cytokines (referred to collectively as "adipokines") which regulate both lipid and glucose metabolism and play a direct role in development of insulin resistance and diabetes. Some of them are peptide hormones such as adiponectin (also Acrp30) and resistin, and proinflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TN-α) [1-7].

Two best-characterized antidiabetic adipokines, leptin and adiponectin have been shown to decrease triglyceride synthesis, promote fatty acid catabolism, and enhance insulin action in both skeletal muscle and the liver. Furthermore, obesity leads to a state of leptin resistance, and one of adiponectin deficiency. Moreover, insulin resistance is associated with increased production of resistin, IL-6, TNF-α, and retinol-binding protein-4 (RBP-4) by adipose tissue, all of which have been shown to induce insulin resistance in muscle and the liver. Leptin infusion ameliorates insulin resistance in lipoatrophic mice, whereas transplantation of fat from leptin-deficient mice into such animals fails to improve insulin sensitivity. Furthermore, leptin administration to humans with severe lipodystrophy partially reverses their severe insulin resistance and hyperlipidemia. Down regulation of GLUT4 and glucose transport selectively in adipose tissue has been shown to cause insulin resistance in muscle, perhaps by diverting FFAs and other fuels from adipose to non-adipose tissues [8-10].

Markers of Insulin Resistance: Elevated Plasma FFA in Type-2 Diabetic State

Postprandial FFA levels are usually higher in obese, insulin resistant individuals and in individuals with type-2 diabetes; elevated plasma FFA levels are independent predictor of progression to type-2 diabetes in Caucasians and Pima Indians.FFA correlated with low insulin-mediated glucose disposal in these individuals, and are associated with an increased risk of myocardial ischemia, and also correlated to carotid intima-media thickness and endothelial dysfunction. FFA enhances basal and insulin-stimulated insulin secretion. However, chronic elevations of FFAs may contribute to peripheral and hepatic insulin resistance, and β-cell dysfunction in type-2 diabetes, and exhibit reduced insulin-stimulated muscle glucose uptake. FFAs induce hepatic insulin resistance in the basal state, which is the cause of impaired insulin-mediated suppression of glycogenolysis. Hence, FFAs increase the *de novo* synthesis of glucose by the liver. Furthermore, FFA also increases the secretion of very low-density lipoprotein (VLDL). Increased levels of FFA reduce glucose-stimulated insulin secretion (GSIS) and decreases β-cell mass as well (β-cell lipotoxicity) [11-18].

Obesity and Type-2 Diabetes

Obesity can be defined as an excessive amount of body fat (body mass index, BMI ≥ 30 kg/m^2). Obesity has been suggested increasing an individual's risk for cancer, gastrointestinal diseases, arthritis, diabetes, and cardiovascular disease. Obesity and insulin resistance are integrally related. Type-2 diabetes and obesity often co-exist together; treatment of both should be initiated together, with lifestyle modifications and pharmacologic therapy. Surgical options, including gastric bypass, are now considered best options which ameliorates both diabetes and obesity [19-21].

Polycystic Ovary Syndrome (PCO) and Metabolic Complications

Recent research trials suggests that PCOS is associated with metabolic complications including obesity, insulin resistance , type-2 diabetes mellitus , hypertension , dyslipidemia , metabolic syndrome , nonalcoholic fatty liver disease and cardiovascular disease. PCOS affects 4–7% of reproductive-aged women. It is characterized by irregular menses and hyperandrogenism. The goal is to manage both the reproductive and metabolic components of PCOS [22-26].

The diagnosis of PCOS requires two of the following three criteria: (1) Oligo- or anovulation (2) Biochemical and/or clinical signs of hyperandrogenism (3) Polycystic ovaries documented by specified ultrasound criteria .The precise etiology of PCOS is still unknown. However, hypothalamic-pituitary axis abnormalities result in abnormal secretion of gonadotropin releasing hormone (GnRH), resulting in an increase in luteinizing hormone (LH), and a decrease in follicle stimulating hormone (FSH), and favoring ovarian over-production of testosterone is hypothesized. Other proposed patho-physiologies include an enzymatic defect of ovarian (or and adrenal) steroidogenesis which favors excess androgen production; and insulin resistance which drives the metabolic and reproductive abnormalities in PCOS [27-31].

It has been demonstrated that hyperinsulinemia (due to insulin resistance) stimulates ovarian theca cells from PCOS women to produce androgens. In addition to insulin resistance, women with PCOS appear to have impaired beta-cell function .Impaired glucose tolerance develops when the beta cell can no longer compensate for the insulin resistance. There is an increased risk of gestational diabetes in women with PCOS [32-34].

Lifestyle interventions are the cornerstone of PCOS therapy. Metformin inhibits the production of hepatic glucose and increases insulin sensitivity. In clinical trials, it has been shown to decrease risk of conversion from IGT to type-2 diabetes. This finding has made metformin a potentially attractive therapy for diabetes prevention in other populations, including those with PCOS. Though metformin can induce ovulation in some women with PCOS, its continued use during pregnancy is controversial and is currently category B and further studies are needed to document its safety during pregnancy.

In PCOS, metformin may decrease androgen levels. Metformin appears to be an effective mode of enhancing ovulation, particularly in combination with clomiphene-citrate, in women with PCOS. Hence, fertility may improve with use of metformin. Beside metformin therapy, other treatment for PCOS include thiazolodinediones, hormonal contraceptive therapy (estrogen-progestin therapy), and anti-androgen therapy (spironolactone, flutamide, finasteride) [35-41].

Recommendations

At tertiary care diabetes centers, all patients should be screened for obesity, dyslipidemia, nephropathy, retinopathy and other diabetic metabolic risk factors to prevent further complications. Clinical guidelines should be used for the management of diabetic patients [42-53].

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