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Short Communication

Insulin Resistance and Obesity

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Introduction

Obesity is an excessive growth of adipose tissue depot due to chronic consumption of calories that exceed the need of energy by an individual. It's a predisposing condition for various non-communicable diseases, like cardiovascular diseases, type 2 Diabetes Mellitus, hypertension, some malignancies, non-alcoholic fatty liver, chronic kidney diseases and sleep apnea syndrome [1]. Overweight and obesity are important risk factors for development of T2DM and found to be associated with Insulin Resistance (IR) in person with normal blood glucose levels also [2]. IR is a well-known fundamental defect and important culprit in obesity related complications and T2DM among all ethnic population in both genders. Obesity and IR usually precede the onset of T2DM. Sedentary lifestyle, excess intake of calories, lack of exercise, psychological stress, genetic predisposition, longer duration of obesity enhance development of IR. Incidence of IR has been reported 48.7% among overweight and 66.3% among obese patients [3]. IR is an independent risk factor for cardiovascular diseases; therefore it is absolutely essential to control it in order to curtail the risk of CV diseases.

IR and Obesity

Insulin is a polypeptide hypoglycemic hormone secreted by β cell of islets of Langerhans of pancreas with multiple physiological actions. It decreases blood glucose levels by various mechanisms like increasing uptake of glucose in Insulin sensitive peripheral cells, stimulation of glycogenesis, inhibition of gluconeogenesis, and glycogenolysis. Glucose homeostasis reflects precise balance between hepatic glucose production, peripheral glucose uptake and utilization. Insulin is the most important regulator of this equilibrium though it is interplay between various neural, hormonal and metabolic signals [4].

IR is a condition in which insulin-sensitive tissues lose response to insulin resulting in hyperinsulinemia, impaired glucose tolerance and hyperglycemia [5]. Systemic IR result from impaired action of insulin in metabolically active organs and tissues like skeletal muscles, liver and adipose tissue. In skeletal muscles, insulin sensitivity is reduced in presence of adipocyte-derived lipids. IR causes impaired insulin-mediated glucose transport and inhibition of lipolysis in adipose tissue [6].

Obesity is a chronic state of low-grade systemic inflammation that causes inhibition of insulin signaling activity in adipocytes and hepatocytes by various mechanisms. Mechanisms proposed for obesity driven IR are- inhibition of insulin receptor substrate-1 and insulin receptor in insulin signaling pathway, inhibition of PPAR γ function and increased levels of plasma free fatty acids by stimulation of lipolysis and inhibition of triglycerides synthesis. IR is associated with hyperinsulinemia, increased concentration of serum insulin in fasting state. High levels of plasma insulin may induce IR especially in presence of fatty acids. In obesity, there is either excess synthesis or reduced clearance of Insulin leading to hyperinsulinemia. β cell function and number in pancreatic islets is increased due to stimulation by glucose/ fatty acids during weight gain. Also Leptin resistance in β cells is responsible for over-production of Insulin [7]. IR in muscle and liver, central etiological factor in causation of T2DM appears to be polygenic in origin.

Even though strong association between obesity and T2DM is a well-established fact, not all forms of obesity are associated with IR. Visceral obesity reflected by high waist circumference or high waist: hip ratio is at high risk to develop T2DM than subcutaneous fat obesity. Several mechanisms have been postulated to link visceral adiposity with IR like inherent diabetogenic property of visceral fat, release of cytokines and adipokines contributing to systemic IR [8]. Dysfunctional Adipocytes and adipose tissue play key role in the pathogenesis of IR in overweight and obese people. Hyperplasia and hypertrophy of adipocytes result in drainage of excess of FFA to liver via portal vein and release of inflammatory cytokines leading to hepatic IR. Spill over of FFA to visceral fat compartment and non-adipose tissues like liver, pancreas, kidney, bone hamper the functioning of involved organs through cell lipotoxicity and apoptosis [9].

Measurement of IR

Insulin insensitivity that is IR is increasingly shown to be an important, serious and widespread mechanism of metabolic derangement among obese and overweight subjects. Assessing insulin sensitivity has not only research or diagnostic interest but also has therapeutic implications. The hyperinsulinemic euglycemic clamp technique is the "gold standard" method for measuring insulin sensitivity. But this method is not fully physiological. Also it is a costly, impractical and technically challenging tool for large-scale use. Insulin suppression test is another way to assess IR, but needs frequent blood samples and analysis, which makes this test cumbersome [4]. Fasting insulin concentration is probably the simplest surrogate marker for IR, but insulin alone can only be considered a reasonable measure of insulin sensitivity in steady-state (basal) conditions and when blood glucose levels are within the normal range [10]. Homeostatic Model Assessment of Insulin Resistance Index (HOMA-IR) is a mathematical model widely used to estimate pancreatic cell function and degree of IR. It is a non-invasive simple tool for clinician that requires only fasting blood glucose and serum Insulin concentrations. It is calculated as product of fasting blood glucose (mmol/L) and serum Insulin (μU/ml) divided by constant. HOMA-

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IR index correlates well with results of euglycemic hyperinsulinemic glucose clamp. Hence it is gaining popularity among researchers as a surrogate marker of IR.

Management of IR

Obesity and IR is a complicated phenomenon that needs prompt management to prevent further metabolic and non-metabolic complications. Weight loss through dietary modification and exercise remains key step in the first line management of IR. Non-pharmacological treatment in the form of adopting healthy lifestyle should be emphasized to the patients for weight reduction. Meticulously planned diet and exercise program is an essential part of the treatment, which should be followed by the patient [11]. Exercise improves insulin sensitivity by increasing oxidative enzymes, GLUT-4, capillari and reducing central adiposity.

Thiazoladinediones and biguinides are class of drugs used in the management of T2DM by improving insulin sensitivity. The Thiazoladinediones group contains the pioglitazone and rosiglitazone. The Rosiglitazone was banned for increased risk of CV mortality. Pioglitazone is a very effective insulin sensitizer but caution has to be exercised in its use due to certain adverse effects. Metformin belonging to the Biguinides group is a safe and well-tolerated insulin sensitizer.

Surgical management of obesity with IR includes bariatric surgery. It is a highly effective therapy which improves adipose tissue Insulin sensitivity with reduction in lipolysis.

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