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EDITORIAL

Hyperinsulenemia, Obesity, and T2 Diabetes: A continuum

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Insulin, an anabolic peptide hormone, is known to have a key role in carbohydrate, lipid, and fat metabolism. It has effects on almost every organ in the body, including adipose tissue, liver, muscle, brain, bone [1], kidneys [2], and vasculature [3]. A variety of mechanisms regulate insulin concentrations by affecting insulin clearance and secretion, through coordinated signals from the hypothalamic–pituitary–adrenal (HPA) axis, the liver–pancreas axis, the entero–osseous axis, and the bone–pancreas axis [4]. Hyperinsulinemia refers to chronically elevated insulin concentration without hypoglycemia, seen commonly in obese individuals as well as those with related metabolic disorders, due to dysregulation of insulin secretion and/or insulin clearance. A rise in fasting insulin levels is seen as an individual progresses from normal glucose tolerance to impaired glucose tolerance (IGT) to T2DM [5]. Obese subjects without diabetes or hypertension show an increased prevalence of hyperinsulinemia and insulin hypersecretion than insulin resistance [6] and hence in such subjects' hyperinsulinemia may rather precede and contribute to insulin resistance. Furthermore, cohort studies have demonstrated that individuals having similar degrees of insulin sensitivity may exhibit a wide range of insulin secretion.

The euglycemic glucose clamp (EGC) and oral glucose tolerance test (OGTT), both are important tools for the assessment of insulin clearance. Hyperinsulinemia is associated with both obesity and insulin resistance [7] and can result from increased insulin secretory capacity and/or reduced insulin clearance. Hyperinsulinemia, especially the insulin levels at 30 min during the OGTT, has demonstrated a causal relationship with obesity.

Prakash SS in his Letter to Editor "Hyperinsulinemia, obesity, and diabetes mellitus" published in this issue explored the difference in insulin resistance in obese and lean individuals. He diligently eluded that obese individuals demonstrate insulin resistance in the adipose tissue resulting in increased lipolysis and lipotoxicity in other tissues including muscle and liver [8, 9]. On the other hand, the progression of disease in the lean individuals could be driven by insulin resistance in the liver leading to inefficient insulin clearance and muscle insulin resistance. The difference between insulin resistance in the liver/muscles and that in adipose tissue could be related to the increased "capacity" of liver and muscle tissues to handle glucose and the increased "capability" of adipose tissue to efficiently store glucose as fat in the context of the whole-body glucose metabolism [9]. Based on these observations, it can be concluded that hyperinsulinemia in obese individuals could be due to increased insulin secretion to compensate for the adipose tissue insulin resistance, ultimately leading to β-cell failure and reduced insulin secretion, whereas in non-obese lean individuals, hyperinsulinemia could be due to reduced insulin clearance secondary to insulin resistance in the liver [8, 10–12].

Hence, the author summarises that in obese T2DM individuals, the main pathogenic mechanism could be the decrease in insulin secretory capacity, while in non-obese individuals, a reduction in insulin clearance leading to hyperinsulinemia is likely to play a major role in the pathogenesis of T2DM. This hypothesis that the onset of adipose insulin resistance in obese individuals and hepatic insulin resistance in non-obese individuals could be the critical events in the progression of NGT and IGT to T2DM lays grounds for future studies exploring these effects in both obese as well as non-obese subjects with or without diabetes.

The study by Vinay Kumar and Sudha Vidyasagar "Association of serum osteocalcin with beta cell function, insulin resistance and glycemic parameters in south Indian type 2 diabetic subjects" published in this issue has explored osteocalcin (OC), also known as bone Gla (gamma-carboxyglutamic acid) protein, which is a marker of bone formation, also currently purported to have a role in glucose and fat metabolism. This study looks at an association of this osteokine with parameters of glucose metabolism in Indian subjects, suggesting a possible role of OC in the pathogenesis of diabetes.

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Reduction in serum OC levels was demonstrated with an increase in insulin resistance (HOMA-IR); however, beta cell function did not show any relationship with OC levels. OC levels further showed a statistically insignificant negative association with FPG levels. Glycated haemoglobin (HbA1c) levels were shown to be significantly reduced in diabetic patients with higher serum OC levels. This study concluded that serum OC was significantly associated with insulin resistance and HbA1c in subjects with T2DM, suggesting a possible role of serum OC in glucose metabolism in T2DM. This study adds another perspective to our understanding of the complex mechanisms involving insulin resistance and opens vistas for future studies looking at the link between bone markers and glucose homeostasis.

The study by Sevil Karahan Yılmaz et al. "Comparison of Inflammation-Related Hematologic Indices For Predicting Metabolic Syndrome in Adults" published in this issue evaluated different hematologic indices (neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), lymphocyte/monocyte ratio (LMR), lymphocyte/high-density lipoprotein to cholesterol ratio (LHR), neutrophil/high-density lipoprotein to cholesterol ratio (NHR), and monocyte/high-density lipoprotein to cholesterol ratio (MHR) associated with inflammation in predicting metabolic syndrome in adults. This study concluded that the NHR index is a strong predictor of metabolic syndrome. In men, the NHR index is a better predictor of metabolic syndrome than the LHR index, and in women, the NHR index is better than both LHR and LMR.

Hyperinsulinemia is commonly associated with obesity, metabolic syndrome, and the early stage of T2DM. There is a need for larger long-term studies to further test the role of hyperinsulinemia as a key driving force in these conditions and to determine its net contribution, which is most likely to be context-dependent. The traditional paradigm, where hyperinsulinemia was considered to be an adaptation to obesity-induced insulin resistance seems to be changing with mounting evidence showing that hyperinsulinemia can precede and eventually cause obesity and insulin resistance.

Summing up, while insulin is an anabolic peptide hormone essential for maintaining normal life and metabolism, the negative consequences of hyperinsulinemia in causation as well as contribution to conditions such as obesity and T2DM shed light on the importance of keeping insulin levels within a healthy target range. Lifestyle interventions or therapeutics with mild insulin-suppressing actions can provide new opportunities to prevent and treat certain disorders like obesity, chronic inflammation, and cancers that have been found to be associated with hyperinsulinemia.

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