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Editorial

Insulin Resistance: From Theory To Practice

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Abstract:
Insulin resistance is at the core of the well recognised metabolic syndrome and possibly many other ailments commonly seen in the modern society. While the quantification of insulin resistance remains a difficult task, the problems associated with it are increasing in epidemic proportions. Need of the hour therefore is to develop concise dietary and pharmacotherapeutic guidelines for prevention and management of insulin resistance.
Key Words: Insulin resistance, Diseases of civilization, Diet

Insulin resistance (IR) is defined as an impaired metabolic response to either exogenous or endogenous insulin, that results in a higher plasma insulin concentration than would be expected for the existing plasma glucose.(1) The lack of physiological response of peripheral tissues to insulin action leads to the metabolic and hemodynamic disturbances known as the metabolic syndrome characterized by dyslipidemia, hypertension, glucose intolerance or type 2 diabetes, hyperuricemia, abdominal obesity, hypercoagulability with impaired fibrinolysis, atherosclerosis, hyperandrogenism, fatty liver and an increased incidence of coronary heart disease.(2-4) Insulin being a well established growth promoting hormone, hyperinsulinemia may favor unregulated tissue growth leading to a variety of problems like acne, early menarche, certain epithelial cell carcinomas, increased stature, myopia, cutaneous papillomas (skin tags), acanthosis nigricans, polycystic ovary syndrome (PCOS) and male vertex balding.(5) Understandably, diseases related to hyperinsulinemia are responsible for substantial morbidity and premature mortality worldwide.(6)

Although insulin resistance can be suspected on the basis of the various clinical disorders associated with it, quantifying it would help in evolving better management strategies, but this remains a challenge. Organizations like the American Association of Clinical Endocrinologists (AACE), National Cholesterol Education Program's Adult Treatment Panel III (ATP III) and the World Health Organization (WHO) have proposed criteria for the diagnosis of insulin resistance syndrome based on the body mass index, blood pressure, blood lipids and blood glucose levels.(7) Even though hyperinsulinemia is central to the pathogenesis of insulin resistance syndrome, measurement of plasma insulin is not included in these criteria. Measuring insulin is limited by the lack of standardization of the insulin assay procedure, controversy as to whether the measurement can accurately indicate the presence of insulin resistance, and the lack of a defined cutoff point to distinguish normal and abnormal levels.(1) Other abnormalities like increased plasma uric acid, decreased renal uric acid clearance, increased plasminogen activator inhibitor 1, increased fibrinogen, elevated high sensitivity C reactive protein, and increased WBC count may also be seen in individuals with insulin resistance.

Insulin resistance can be quantified *in vivo* with methods such as the pancreatic suppression test, the hyperinsulinemic-euglycemic clamp technique and the minimal model approximation of the metabolism of glucose (MMAMG).(4) In the euglycemic insulin clamp technique, exogenous insulin is infused to maintain a constant plasma insulin level above fasting and the insulin-resistant patient requires much less glucose to maintain basal plasma glucose levels.(1) The minimal model analysis involves frequent sampling of glucose and insulin from an indwelling catheter during an intravenous glucose tolerance test and calculation of the index that reflects insulin sensitivity by

a computer model. Although the MMAMG compares well with the euglycemic insulin clamp test, its application is limited by the need for endogenous insulin secretion.(8) The cost, time and complexity involved makes it difficult to utilize these tests in routine clinical practice.(8)

For epidemiologic and clinical studies, more simple, indirect methods have been advocated for quantification of IR like the Homeostasis Model Assessments (HOMA), Quantitative Insulin Sensitivity Check Index (QUICKI), and McAuley index (McA).(4,9) HOMA and QUICKI indices are calculated using both the fasting insulin (FI) and fasting blood glucose levels. McA is calculated using FI and fasting triglyceride levels.(9) These indirect indices of IR, particularly the McAuley index, have shown a good correlation with the MMAMG index.(4)

Research into the causes of insulin resistance and its various consequences has thrown up many interesting hypotheses and revealed many inter-related pathophysiological changes (10-17) that could have spiraling effects in patients with metabolic syndrome. But due to the difficulties of defining insulin resistance in clinical terms and of quantifying insulin action in humans, the actual prevalence of insulin resistance world wide is unknown.(6) Therefore, recommending interventions for the great number of sufferers of these diseases of civilization would have to be on the basis of the various clinically identifiable disorders, at least for the time being, so that the exploding epidemic could be curtailed.

Need of the hour is to develop concise guidelines for prevention as well as treatment of the metabolic syndrome on the basis of the available information. In this context, diets that intend to reduce hyperinsulinemia deserve a serious consideration. Dietary interventions utilizing low-glycemic, high fibre carbohydrates may be useful in preventing and treating all diseases of insulin resistance.(5,17,18) Metformin has been shown to lower the risk of myocardial infarction and all-cause mortality by more than 30% in patients with type 2 diabetes and obesity, as well as having a beneficial effect on the lipid profile.(10) Avoiding drugs such as ß blockers and high dose thiazides that exacerbate insulin resistance and instead using angiotensin converting enzyme inhibitors and alpha blockers that may reduce resistance (6) should also be emphasized.

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