Insulin Resistance: A Metabolic Mystery

The decreased ability of insulin to act effectively on peripheral target tissues (muscle, liver and fat), compared to a normal people is called insulin resistance. It is the decreased biological response of insulin i.e. more insulin would be required to elicit a desired response. Experimentally, it is detected by 'Euglycemic clamp' method where both glucose and insulin are infused simultaneously keeping blood sugar constant. It is observed that more insulin is required for a fixed amount of glucose disposal compared to what is needed in a normal individual. Insulin has two streams of functions, one is metabolic leading to glucose, fat and amino acid storage into cells; another poorly understood stream of action is mitogenic that controls cell growth and differentiation using mitogen activated protein (MAP) kinase pathway. Insulin resistance is primarily a post-receptor defect of metabolic signaling pathway, resulting in reduced glucose transport into cells. But mitogenic pathway is spared. Insulin resistance is a relative term, since supernormal level of circulating insulin can normalize the plasma glucose. Hyperinsulinaemic state can store nutrients into cells and decreases hepatic glucose production, but impaired muscle uptake persists. Though the capacity of glucose disposal is reduced by 30-60%, it is compensated by hypersecretion of B-cell mass which may eventually fail to function from over exhaustion. So, the consequence is the gradual evolution of impaired glucose tolerance (IFG, IGT) and diabetes.

In insulin resistant state, hyperinsulinaemia keeps patient euglycaemic for a prolonged period but accelerates diabetic and non-diabetic conditions such as atherosclerosis. Other conditions, as described later, may also ensue. Genetic susceptibility and obesity of any aetiology contribute to insulin resistance by offering free fatty acid (FFA) to plasma. FFA impairs B-cell function, reduces glucose uptake by muscles and promotes glucose production by liver leading to impaired fasting glucose. Ageing, steroid and other hormones offer post-receptor blocking of insulin action. So, hyperglycaemia is a readily detectable feature of insulin resistance, IFG, IGT or type -2 diabetes mellitus all included.

Metabolic syndrome, a very common condition (present in 20% of US adults), is associated with accelerated cardiovascular disease. All aspects of this syndrome can be explained by insulin resistance as pivotal player. Polycystic ovarian syndrome (PCOS) is very common and can be treated by drugs that reduce insulin resistance, metformin and thiazolidindiones are examples. Severe insulin resistance syndromes are rare but interesting. Type - A insulin resistance syndrome has defect in insulin signaling pathways. Type - B syndrome has anti-receptor antibody in circulation, stimulatory or inhibitory. Hyperandrogenism, a common factor to these

three syndromes, is due to ovarian theca cell mass stimulation by insulin and insulin induced SHBG reduction. It is worth mentioning here that insulin resistance is also considered to be the principal metabolic abnormality in inflammatory conditions. The finding was evaluated among rheumatoid arthritis patients in Bangladeshi population and is reported in the current issue of this journal. Hyperinsulinaemia as a marker for coronary artery disease risk, syndrome X, PCOS and various other rare diseases adds to the recent interest in this metabolic mystery, the insulin resistance.

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