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Measurement of Insulin Resistance in Vivo

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Insulin resistance is defined as a subnormal biological response to endogenous or exogenous insulin. This subnormal biological response is considered for ability of insulin to decrease the blood glucose. However, the dose of insulin for optimal biological response is quite variable and has marked intra- and interindividual variations (1). In clamp studies it has been shown that subjects who are obese but non-diabetic are insulin resistant and it progressively increased with occurrence of glucose intolerance (1). It has been also described that the minimum amount of physiological concentration of insulin is required for prevention of ketosis, whereas the maximum amount of insulin concentration is required for muscle glucose uptake. The clinical markers for insulin insensitivity include BMI>25kg/m^2 , waist line>102 cm in men and 88 cm in women, acanthosis nigricans and skin tags (2).

Insulin resistance in vivo can be measured by a computerized based model named as Homeostatic Model Assessment (HOMA) assessing insulin resistance at periphery called as HOMA-IR and at β-cell called as HOMA-β.[3] It provides an idea about the basal insulin resistance where the formula for HOMA- IR includes FPG (mmol/L)x IRI(μU/ml) /22.5 and formula for HOMA-β is 20 x IRI (μU/ml) / FPG(mmol/L) -3.5. The HOMA correlates with clamp studies and is good for epidemiological surveys. Another test is short insulin tolerance test where insulin is injected at a does of 0.1 U/kg body weight as IV bolus and samples for glucose are taken at 15 and 5 minute before and 3, 6, 9, 12, 15, 20 and 30 minutes after insulin injection (1). The rate constant for plasma glucose disappearance is calculated from the formula 0.693/T ½ and the plasma glucose T ½ is calculated from the slope of the least square analysis of the plasma glucose concentration from 3-15 minute after IV insulin injection. The other method to assess insulin resistance is oral glucose tolerance test which includes following ingestion of 75 gm of glucose, plasma glucose and insulin samples are taken at 0,30,60,90,120 minutes. It correlates with hyperglycemic clamp technique ($r=0.67$, $p< 0.05$). The clamp studies are the 'gold standards' for assessing insulin resistance both at β cell as well as in peripheral tissues (4). The euglycemic clamp technique assesses peripheral insulin resistance where glucose is given at a variable rate with the aim of maintaining plasma glucose at or

between 90-110 mg/dl and insulin is given at a fixed dose infusion. Samples for blood glucose are collected at 3-5 minute interval and insulin resistance is calculated by one upon the amount of glucose infused to maintain the steady state. Similarly the hyperglycemic clamp is used to assess the β cell secretory function where glucose is infused at variable rate with the aim to keep the plasma glucose between 180-200 mg/dl and at a steady state sample for glucose and insulin are taken and glucose insulin ratio gives the value of resistance at a β cell level (4). The clamp studies are 'gold standard' to assess insulin resistance but they are invasive, expensive and requires a lot of efforts, therefore, these are used only for research purposes. However, in clinical practice, HOMA and insulin tolerance test are good modalities to assess insulin resistance (1).

The insulin resistance is associated with various metabolic abnormalities including visceral adiposity, hypertension, impaired glucose tolerance and dyslipidemia and virtually all these are surrogate markers of insulin resistance. ATPIII and WHO both have defined the insulin resistance (2) syndrome by including these parameters and at least 3 of them have to be present for a diagnosis of insulin resistance syndrome(IRS).

The abdominal or visceral adiposity is the hallmark of insulin resistance syndrome and whether it is a cause or effect of insulin resistance is a million dollar question (5). Possibly the visceral obesity is influenced by genetic factors to begin with and later on environmental factors predominate. The waist circumference of more than 102 cm in men and more than 88 cm in women has been defined as detrimental (6,7). The other putative mechanism for abdominal obesity include increased 11-beta hydroxysteroid dehydrogenase type 1 activity which converts cortisone to cortisol, that by inducing lipoprotein lipase activity results in increased visceral fat (6). Hyperinsulinemia as a consequence of insulin resistance also increases visceral fat (6). Visceral fat being more metabolically active and rich in blood and β_3 adrenergic supply results in excess release of free fatty acids (FFAs). FFA's not only result in impaired insulin action at target tissues including muscle but impaired insulin secretion by β cells (8,9). Impaired insulin action at muscle is largely attributed to interference with insulin signaling mechanism including tyrosine kinase and PI3 pathway (10). Similarly impaired insulin secretion is due to decrease in glucose uptake and utilization by the β cells thereby requisite amount of ATP is not produced resulting in decreased insulin secretion (9). These effects of FFA's are collectively called as lipotoxicity. Increasing insulin resistance progressively affects the β cell function and subsequently results in inexorable β cell exhaustion (12). Hypertension associated with insulin resistance is attributed to lack of insulin mediated vasodilatation because of decreased nitric oxide synthase (NO synthase), insulin mediated increased

absorption of sodium from the renal tubule, increased sympathetic nervous system activity and increased angiotensinogen and angiotensin converting enzyme activity from adipocytes are other contributory factors for hypertension (2). The glucose intolerance associated with insulin resistance is the result of increased insulin secretion from the beta cells subsequent to insulin resistance and later on leading to beta cell exhaustion and occurrence of hyperglycemia (13). The dyslipidemia associated with insulin resistance is characterized by increased VLDL, increased small dense LDL and decreased HDL. These abnormalities of lipid profile are consequent to impaired lipoprotein lipase (LPL) activity, increased hormone sensitive lipase (HSL) activity, and decreased degradation of LDL leading to their longer stay in circulation and making them vulnerable to become small dense LDL (10).

Therefore, insulin resistance is the characteristic abnormality of insulin resistance syndrome and various clinical and biochemical predictors are surrogate markers of it. It has a relevance in predicting the future onset of T2DM and cardiovascular diseases.

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