Insulin Resistance (IR) in Impaired Glucose Tolerance (IGT)

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Issues relating the methodology of measurement of insulin resistance (IR) often confound the issues of IR in impaired glucose tolerance (IGT).

Impaired pulsatile secretion of insulin in relatives of patients with non-insulin-dependent diabetes mellitus was described as an early pathogenetic phenomenon[1]. Moreover, impaired action of insulin (insulin resistance) has been associated with pre-diabetic state, impaired glucose tolerance and diabetes mellitus[2]. It is postulated that IR then leads to insulin deficiency. Thus, glucose intolerance develops either as a result of secondary beta-cell failure in a backdrop of insulin resistance (often designated as “beta-cell exhaustion”) or as a result of primary beta cell defect. Whether primary or secondary, poorly functioning beta-cells cannot be relied upon to provide insulin while estimating insulin resistance. However, basal or post-stimulation insulin levels tend to rise with rising insulin resistance(to maintain euglycaemia), the level will not be reflective of IR in presence of beta-cell defect. This occurs in the presence of glucose intolerance. Moreover, by definition of glucose intolerance, the glucose levels achieved on (only) glucose infusion/ingestion would be higher in these conditions. Since hyperglycaemia itself has been implicated in the development of IR, an estimate of IR at different ambient glucose levels cannot be strictly compared. On the issue of methodology of IR, there have been two elegant reviews published recently[3,4].

The methodology to determine IR should satisfy at least six requirements.

1. The insulin levels achieved during the study should be enough to stimulate glucose metabolism and the insulin concentration should be able to suppress the hepatic glucose output, (HGO) reliably, this (figure 1) requires 30-40 uU/ml in non-IR states and above 80-100 uU/ml in the IR states. In the absence of adequate insulin concentration, if the HGO is not fully suppressed, the liver will continue to be a source of glucose, besides the infused glucose. Thus, the total body utilisation of glucose as estimated by infusion rate (M value) may be grossly underestimated and the IR overestimated. Several methods like CIGMA (continuous infusion of glucose with model assessment) achieve insulin concentrations between 10-20 uU/ml.

2. The insulin level achieved should be able to stimulate glucose utilisation enough to pick up differences between IR and non-IR -group. This, as shown in figure 1 will not be possible in methodologies associated with low insulin concentration as discussed[3]. When insulin levels reach a concentration of 100 uU/ml, the studies would be able to demonstrate a 10% difference in M value.

Fig. 1 : Relationship of Hepatic Glucose production, plasma insulin and glucose disposal

Moreover, once beta-cell deficiency sets in, methodologies that rely on endogenous insulin secretion would face more and more problems of relative inadequacy of insulin. CIGMA and Minimal model (Bergman’s model) fare well in normal glucose tolerant individuals, whereas their utility in IGT or clinical diabetes mellitus is not clear. Once modified with added exogenous insulin, the Minimal model overcomes the problem of insulin deficiency in IGT up to a certain extent.

3. The insulin levels achieved should not be so high so as to mask the IR induced by receptor defects seen early in the evolution of glucose intolerance. A reduction in insulin receptors would only cause a decreased responsiveness, however, the maximal response achieved would be similar at a higher insulin concentration (figure 2).
4. The measurements carried out under conditions of changing glucose and insulin levels would alter the insulin secretion, insulin action and secretion of the counter regulatory hormones. This may blur the real differences, if any, between the groups studied especially in those who have subtle changes in insulin sensitivity. Thus, it may be pertinent to do IR studies in IGT in a steady state. Minimal model, hyperglycaemic clamp, insulin tolerance tests are a few examples of methods for estimating insulin resistance in a non-steady state.

5. The presumption of the models should be fundamentally sound. The Minimal model of Bergman presumes that glucose kinetics is monocompartmental and insulin action takes place in a remote compartment. Both these assumptions are based on shaky foundation.

6. The glucose utilisation estimated should be at a more or less physiological level. The glucose utilisation is a function of ambient glucose concentration. In glucose intolerance, the glucose level achieved may be sufficient to push itself intracellular under the so called mass effect (glucose mediated glucose disposal). Thus, the methodologies using solo glucose infusion to achieve hyperglycaemia would erratically (under) estimate the level of IR.

To satisfy all the above criteria, hyperinsulinaemic euglycaemic clamp (HEC) is the most appropriate method to estimate IR in subjects with glucose intolerance. A recent and elegant study done by Saad, Anderson, Laws and others [5], has shown that insulin modified frequently sampled intravenous glucose tolerance test (FSIGTT) can be used as a simple test for assessment of insulin sensitivity in population studies involving non-diabetic subjects. The insulin sensitivity estimated by this (22 sample FSIGTT method) correlated best with NGT (r = 0.53), less with IGT (r = 0.48) and least with NIDDM (r = 0.41). Fasting and post-load insulin levels have also been used for estimating IR in large studies. In another elegant study published recently, Laakso answered the question ‘How good a marker is insulin level for insulin resistance?’ [6] Though the fasting and post-glucose load insulin levels correlated significantly with euglycaemic clamp in NGT (r = 0.66 and -0.68, both p<0.01), they were not as reliable in IGT {r=-0.47 (p<0.05) and -0.39 (ns)} nor in NIDDM {r=-0.48 p<0.05 and r=0.15(ns)}. In brief, though the studies for IR in normal glucose tolerant individuals can be carried out using simple methodology, once in the arena of glucose intolerance, it becomes increasingly important to estimate IR using the gold standard hyperinsulinaemic euglycaemic clamp.

**Insulin resistance and glucose intolerance**

Insulin resistance (IR) as well as insulin deficiency (ID) have been shown to be strong predictors in the future development of Type 2 diabetes mellitus. With a relative hazard of 31.1 (95% CI:4.9 - 197.1) for IR (M value at insulin concentration of 130 uU/ml) and 15.8(95% CI: 5.4 46.7) for ID, IR seems to be highly predictive of Type 2 DM[7]. Eriksson and his co-workers [8] studied the first degree relatives of patients with type 2 diabetes. They had four groups of subjects.

1) the index cases (NIDDM).
2) healthy controls without a family history of diabetes.
3) first degree relatives of group 1 with normal glucose tolerance and
4) first degree relatives of group 1 with glucose intolerance.

The controls and the relatives were of similar age, however, BMI was slightly higher among diabetics and relatives with IGT. Relatives with IGT had a slightly higher fasting plasma glucose and a higher concentration of fasting serum insulin. The total glucose metabolism was impaired equally in both the groups of relatives. This reduction was almost completely accounted.
for by the reduction in glycogen synthesis and was similar to the NIDDM subjects. The difference in insulin secretion on hyperglycaemic clamp could account for the difference in the glucose tolerance.

In a similar study [9] on 19 to 29 year old off springs of diabetics, we demonstrated a very high prevalence of diabetes even at that young age. The insulin sensitivity (M value on hyperinsulinaemic euglycaemic clamp) correlated with the glucose tolerance. Also, insulin secretory response to a glucose load was lower with development of glucose intolerance.

Haffner et al [10] while addressing the question "Does the Clock for coronary heart disease start before the onset of clinical diabetes?" demonstrated that confirmed pre-diabetics have a high total and LDL-cholesterol, triglyceride, fasting glucose and insulin, 2-hour glucose, body mass index and blood pressure and a lower HDL - cholesterol. Insulin resistance and hyperinsulinaemia have been demonstrated repeatedly to be associated with high cardiovascular risk factors. [1].

Summary

In summary, data suggests that to eliminate the increased risk of coronary heart disease in populations, a subject at high risk of diabetes should probably be considered to belong to the same category as clinical diabetes. They have a higher degree of insulin resistance, hyperinsulinaemia and coronary risks similar to diabetics. A high risk approach should hence be used for these individuals.

REFERENCES


