

Insulin Resistance and Left Ventricular Mass in Hypertensives

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Till the 1980's to clinicians, insulin resistance was a clinical entity in which there was resistance to exogenously administered insulin predominantly due to insulin antibodies which developed due to use of impure insulins.¹ After the famous Banting lecture by Gerald Reaven in 1987, in which insulin resistance was proposed for the first time as the unifying factor for a host of metabolic abnormalities, the concept of "Reaven's syndrome", or "Syndrome X" or the "Insulin resistance syndrome" was born.²

In the insulin resistance syndrome, hypertension is one of the important constituents. The association between insulin resistance and hypertension was recognized in 1996 by Welborn *et al.*³ Abnormalities of glucose, insulin and lipoprotein metabolism are common in patients with hypertension. Indeed, these changes can also be detected in normotensive first degree relatives of hypertensive patients.

The prevalence of insulin resistance in patients with hypertension may be as high as 50% and although it is more common in the obese, it is also present in non-obese subjects with hypertension.⁴ Insulin resistance is a prohypertensive and vasculotoxic state that may damage the endothelium rendering it more prone to the development of atherosclerosis. Insulin may increase blood pressure by mechanisms such as sympathetic nervous system stimulation and enhanced sodium reabsorption by the kidneys.⁵

Hyperinsulinemia, especially in the fasting state, is considered a surrogate marker of insulin resistance⁶ and values of fasting and post oral glucose serum insulin levels are often taken as clinical markers of the magnitude of insulin resistance. Insulin resistance can also be derived using the homeostasis assessment model (HOMA) where fasting insulin and fasting glucose values are taken into the equation for calculating insulin resistance.⁷

The gold standard for investigation of insulin resistance however, is the hyperinsulinemic euglycemic

insulin clamp technique, where insulin sensitivity of the individual is measured by infusing insulin at a pre-defined rate and maintaining euglycemia by infusing glucose.⁸ The quantity of glucose infused to maintain a stable basal glucose level during specific insulin infusion rates provides an assessment of insulin action.

In the study by Dr. Kunal Kothari *et al* reported in this issue of JAPI, the authors used a two hour post oral glucose load serum insulin level as a marker for insulin resistance and studied the influence of insulin resistance on left ventricular mass in hypertension patients. It is well known that hypertension itself leads to an increase in the left ventricular mass.⁹ Left ventricular hypertrophy is present in 15-25% of patients with hypertension. Moreover, left ventricular hypertrophy (LVH) is recognized as one of the most important predictors of adverse cardiovascular outcomes. The link between adverse cardiovascular complications and LVH in patients with hypertension has not yet been fully explained. LVH associated with hypertension differs from that initiated by other pressure overload related diseases in that its development and regression is the result of hemodynamic and hormonal factors. There is some data to suggest that LVH development is influenced by the renin angiotensin system. Many humoral substances have also been implicated in promoting left ventricular hypertrophy and these include epinephrine, thyroid hormones, adrenal and sex hormones, a number of peptides and cellular proto-oncogenes.¹⁰

Recent experimental evidence suggests that hyperinsulinemia may be linked to the atherosclerotic vascular disease - the insulin-atheroma hypothesis.¹¹ The evidence for insulin as a risk factor for ischaemic heart disease (IHD) in healthy middle aged men is based on various prospective studies which showed a strong correlation between hyperinsulinemia and prevalence of IHD.^{12,13}

Left ventricular hypertrophy might be a manifestation of insulin resistance which predisposes a hypertensive individual to an increased risk of cardiovascular disease. The association of insulin resistance

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and left ventricular hypertrophy has been recently analysed in various studies. The study by Kothari *et al* also demonstrates the association between post oral glucose insulin levels and left ventricular hypertrophy. However as the number of patients enrolled in the study was small, this probably explains why there was not much difference between obese and non obese individuals. It would have been nice if the authors had used fasting insulin levels and calculated insulin resistance using the HOMA model. It would have been even better if clamp studies had been done at least on a subset of these individuals as the results would then have been more conclusive.

How does all this relate to us as Indians? It is well known that Indians have higher plasma insulin levels than weight matched Europeans, both diabetics and non-diabetics.¹⁴ Euglycemic clamp studies have shown that Indians have a higher degree of insulin resistance compared to matched groups of Europeans.¹⁵ Indians have also been shown to have a clustering of cardiovascular risk factors.¹⁶ This stresses the need for detection and correction of insulin's resistance by a combination as diet, physical exercise and weight loss, particularly a reduction in central obesity or the waist hip ratio.^{6,17} This could lead to a marked reduction in insulin resistance and thus help to control hypertension better and prevent or reduce cardiovascular risk.

In summary, insulin resistance is not a single entity but a conglomeration of other features of syndrome X like hypertension. More and more characteristics like left ventricular hypertrophy are being added to the list of abnormalities in this syndrome. The latest is the link of insulin resistance to atherosclerosis through inflammation and the role of cytokines.¹⁸ The presence of one abnormality of "Syndrome X" predicts the appearance of others over time. Specific drugs are now becoming available to improve insulin resistance (eg. insulin sensitizers) and thus probably reduce the prevalence of hypertension and left ventricular hypertrophy which might go a long way in reducing the adverse cardiovascular outcomes associated with this syndrome.

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