Making a case for targeting insulin levels in metabolic (insulin resistance) syndrome

Mathew K. Jose

7A Link Manor, Kochi - 682 018, Kerala, India

It is time to look beyond lifestyle changes, control of glucose, lipids and blood pressure for cardiovascular disease (CVD) risk reduction. Should we be looking at insulin levels? Accumulation of insulin or hyperinsulinemia is largely an attempt by the body to overcome the state of reduced insulin sensitivity in the tissues involved in glucose homeostasis. Though glucose homeostasis may be achieved by pharmacological measures, it does not seem to translate into significant CVD event reduction unless there is concomitant reduction in the raised insulin levels due to insulin resistance (IR). Does IR affect all aspects of insulin action or does it differentially affect the downstream signal pathways? There is a new concept supported by experimental studies of 'selective IR.' These experiments looked at impaired progression of signals through PI3 kinase pathway and possible greater progression through the MAP kinase pathway, eliciting greater response of the downstream targets from the compensatory hyperinsulinemia. Unimpaired MAP kinase pathway may contribute to the pro-atherogenic milieu in metabolic syndrome (MetS). Targeting insulin levels by drug therapy is needed as lifestyle measures are not sustainable in the long term.

KEY WORDS: MAP kinase pathway, metabolic syndrome, selective insulin resistance.

Introduction

There is a finite limit to CVD benefit from glucose and LDL reduction in spite of the evidence from recent studies for aggressive therapy in high risk CVD situations such as coronary heart disease (CHD) and type 2 (T2) diabetes mellitus (DM). However as shown by the Reduction of Atherothrombosis for Continued Health (REACH) Registry[1] we are living in a world where even proven and easy to administer health interventions are not in place in many countries. The investigators who collected data from 44 countries to determine athero-thrombosis risk factor prevalence and treatment, showed that there are similar risk factor profiles and comparable rates of under treatment with statin, anti-platelelets, under treatment of hypertension and failure to diagnosis hyperglycaemia and impaired fasting glucose in the countries studied. Results from the Kupio Ischemic Heart Disease Risk Factor Study[2] reveal that the RR for CHD and total mortality was higher in men with MetS, compared with those who did not have MetS. The Heart Disease Prevention Program, a US-based study in adults, showed that CHD, CVD and total mortality are significantly higher in those with than without MetS/IRS.[3] A window of opportunity for CVD prevention will be lost if we fail to recognize MetS in our patients or if our therapy is not satisfactory.

Correspondence to **Mathew K. Jose**, 7A Link Manor, Kochi - 682 018, Kerala, India. E-mail: matjose@vsnl.net

Discussion

Insulin resistance (IR) is fundamental to high risk CVD situations and the surrogate marker for IR, though not consistently, is high fasting and post-challenge insulin levels. Hence therapeutic insulin reduction must be a logical approach to prevent T2 DM and CVD. Diabetes clearly influences the incidence of CVD with poor outcomes. Studies show that for any level of other risk factors analyzed, a mechanism, or mechanisms, unique to or heavily represented in diabetes/IGT/IFG/MetS makes them more prone for CVD. Hyperglycemia is the most prevalent feature in diabetes and hence it is reasonable to assume this is an independent risk factor for CVD, and euglycemia should control the excess risk. However, the UKPDS[4] showed a decrease of only 16% in macrovascular disease from tight glucose control, and

this did not reach statistical significance. But the study revealed a significant improvement in macrovascular complications by reducing the CVD events among obese diabetics on metformin.[5] This must be derived from something more than its glucose-lowering ability. In other words, metformin-induced improvement in insulin sensitivity with a concomitant decline in insulin was much more potent in reducing CVD problems than an equally significant reduction in glucose levels without reduction in insulin levels. The recent diagnostic revision of IFG by the expert committee[6] is recognition of the future metabolic risks even at low glycemic levels. However, studies do not reveal strong association between IFG and CVD; instead they correlate with post-challenge glucose[7-9] and post-challenge insulin levels.[10] Similarly in lipid therapy, indications are broad and target levels are getting lower and lower. But in the heart protection study (HPS),[11] simvastatin treatment reduced absolute risk of coronary event in the DM / MI cohort by only 4.4%, a 12% reduction in RR in comparison with diabetes-free MI cohorts, who had 5.7 reduction in absolute risk (25% in RR reduction) on simvastatin. During the trial, 22.5% of the non-DM / CHD patients on placebo had repeat MI. But in the DM / MI cohort, 37.8% who received placebo and 33.4% who received statin had repeat MI. Hence even when the diabetic MI survivors were receiving statins, they were at greater relative risk for another coronary event than nondiabetics with coronary history who were on placebo. Now the recommendations are for aggressive lipid lowering, aiming for LDL cholesterol at 2.0 mmol / L (77 mg / dl),[12] and the revised NCEP ATP111[13] recommends a target of <1.8 mmol / L (70 mg / dl) in the very high vascular risk situations.

This limitless revising of targets for LDL, blood pressure and glucose suggests we are not probably getting the results we were hoping for in CVD prevention. Considerable scientific evidence is now available that MetS / IRS is associated usually with hyperinsulinemia and contributes to CVD risk. Is it time now to look more closely at insulin assays, CVD risks from excess insulin and, if it could be, a target for intervention? Insulin has always been a friend through the development of human race, being the best known anabolic hormone. The 'thrifty genotype' has enabled our race to survive through times of adverse food supply by our ability to store food during times of plenty. Due to our tendency to override warning signals in balancing energy intake and expenditure, along with the ease of availability of food in this modern age, this genotype has no survival advantage now. Many attribute the present day epidemic of obesity and T2 DM to this genotype, with suggestions of fetal programming as one cause. Is insulin an enemy? Yes, it can be, at extremes of glycemia, though at differing speeds and ill effects. Under conditions of glucose excess, hyperinsulinemia represents a physiological state in which there is reduced biological action of insulin. The accumulation of insulin, or hyperinsulinemia, is largely an attempt by the body to overcome the reduced insulin sensitivity in the tissues involved in glucose homeostasis. Though glucose homeostasis may be achieved by pharmacological measures, it does not seem to translate into significant CVD event risk reduction unless we achieve concomitant reduction in the raised insulin levels accumulated by physiological compensatory mechanism to overcome IR. The resulting hyperinsulinemia is the key feature of MetS / IRS,[14] and there are newer insights into its role in promoting accelerated atherosclerosis and CVD risk. Although insulin is also involved in lipid and protein metabolism, it is the defective whole body utilization of glucose which is indicative of insulin resistance. The gold standard for assessing IR is by hyperinsulinemic-euglycemic clamp study, and the whole body glucose disposal rate is called the 'M' value. HOMA-IR is a mathematical model that calculates insulin resistance from a measurement of fasting plasma and insulin levels. Although insulin assay is not standardized and has much variability, HOMA-IR is a practical way to assess IR. However, 'M' values and plasma fasting insulin levels do not correlate well in many studies, indicating 'plasma insulin levels' is not a consistent surrogate marker for IR. From the EGIR (European Group for the study of Insulin Resistance) data revealed by Ferrannini,[15] there were 562 subjects with hyperinsulinemia and 493 subjects with insulin resistance on clamp study, yet there were only 288 subjects with IR on clamp study also being hyperinsulinemic. In the San Antonio metabolism study, among 286 individuals 142 had hyperinsulinemia and 182 had IR, yet only 122 had both. What is more obvious in these studies is that plasma insulin correlates with obesity and WHR and IR with TG and FFA levels. EGIR data show that men and women have an association with hypertriglyceridemia and IR, suggesting increased hepatic triglyceride synthesis. The data also showed lower insulin levels in lean individuals with IR, probably due to faster clearance.

Analysis from the Framingham Offspring Study[16] suggests a central metabolic syndrome with high TG, low HDL, high WHR, BMI and fasting and 2-h insulin

levels, with overlapping but separate clusters of hypertension (closely associated with BMI) and hyperglycemia (closely associated with fasting and 2-h insulin). Overall analysis from the above studies appear to suggest that IR is commonly associated with hyperinsulinemia, reflecting beta cell compensation, but they are separate phenomena with both contributing to the phenotype of MetS /IRS, and the dyslipidemia of high TG with low HDL appears central to it.

There is enough scientific evidence that in IR, the defect appears to lie in the insulin signal cascade or signal transduction. A recent discussion[17] on the molecular mechanism of IR which impacts on cardiovascular biology deserves due consideration. Experimental studies[18,19] are introducing a concept of 'selective insulin resistance,' suggesting both reduced and increased action of insulin on downstream signal pathways in IR. One of the pathways is through tyrosine phosphorylation of insulin receptor substrates 1 and 2, which activate PI-3 kinase. This pathway is absolutely necessary for mediating the metabolic effects of insulin. Reduced activation of PI3 kinase is the *sine qua non* of MetS. A second signaling pathway involving phosphorylation of Ras, Raf, MEK and MAP kinases (ERK 1 and 2) contributes solely to the nuclear and mitogenic effects of insulin and plays no role in the metabolic actions of insulin. The studies seem to confirm greater progression through the Shc-Ras-MAP kinase pathway, even eliciting greater response of the downstream targets from the compensatory insulinemia. Insulin has anti-inflammatory and anti-atherogenic properties,[20,21] which are mediated through the PI3 kinase pathway. IR tends to block PI3 kinase dependent signaling, which in turn tends to accelerate both inflammation and atherosclerosis. This is further enhanced by the MAP kinase pathway through activation of prenyltransferases by insulin,[22,23] as IR does not seem to block this action of insulin. Hyperinsulinemia-induced prenylated Ras and Rho resulted in augmentation of cellular response to IGF-1, EGF, PDGF and AT2,[24] causing vascular proliferation. Hyperinsulinemia doubled the ability of AT2 to activate NF-kappa B, a pro-inflammatory nuclear factor in vascular smooth muscle cells.[25]

The benefits of ACE and ARB beyond blood pressure reduction have been proven through many large studies (HOPE,[26] LIFE,[27] etc.) in high risk CVD patients. Post hoc studies have shown reduction of new onset of T2 DM with the use of ACE or ARB in hypertensive patients. This is now being investigated by the ONTARGET program[28] with an ARB. Aggressive lipid management has considerable evidence from studies showing benefits beyond usual levels of LDL reduction. Could there be benefits beyond glycemic control from OHAs?[32] Following the recent worldwide definition of MetS by the IDF,[33] there is clarity in the diagnostic criteria with more emphasis on ethnicity-specific waist circumference (WC) and less on plasma glucose or urinary albumin. With high prevalence even among low income and health resource poor nations such as India,[34] this diagnostic clarity should encourage early initiation of therapeutic lifestyle changes (TLC) such as diet, exercise and weight loss. Despite trial and epidemiological evidence of benefit,[35-40] TLC is not sustainable in the long term due to behavioral, biological and environmental factors. Unless there are drastic changes in the way we legislate and regulate food and beverage industry, obesity is going to be a timeless pandemic. There are advocates for an 'ecological' approach to obesity by tackling the 'obesogenic' environment.[41] The question for many treating physicians faced with an individual who has MetS/IRS with borderline risk components and poor adherence to TLC is, What to do next? Awaiting the individual risk components in MetS/IRS to reach categorical risk level may mean delaying treatment to the time when irreparable tissue damage has taken place. Focusing on the individual components alone for MetS disregards the unifying effect of IR on these components[42] and the underlying concepts for CVD risk in the metabolic state of IR. The option for a laboratory diagnosis[43,44] can be incremental to the criteria and may help in monitoring therapy. A recent study disputed if the addition will capture any more risk independently beyond the diagnostic criteria.[45] Also there are pitfalls in interpreting HOMA-IR due to variability of beta cell response. Further, fasting glucose and insulin levels may not represent the insulin-mediated glucose uptake in all the insulin-sensitive tissues. Difficulties in developing a uniform standardized assay are also seen due to the variable presence of pro-insulin and split products. The hyperinsulinemic-euglycemic clamp method for assessing IR is too time consuming as a practical clinical tool and is unnecessary except in research situations. As an epilog to the IDF criteria, there are suggestions that high WC alone is sensitive to the presence of IR[46] and the other components make the criteria less sensitive as a screening test in nondiabetic population. The recent INTERHEART study[47] involving 52 countries showed WC alone as a significant risk factor for the incidence of MI. Although WC is now accepted as clear indicator of future CVD risk, the concern at an individual level is

specificity and hence requires use of the full criteria to diagnose MetS / IRS. This is more so with Asian Indians, where predictability of Mets / IRS is considerably poor without the biochemical and blood pressure criteria even after using the IDF criteria for WC at >90 cm and >80 cm for men and women respectively.[48] But it is also time we agree that hyperinsulinemia is not an innocent bystander but is causal for atherosclerotic CVD in the syndrome and needs therapy aimed at its reduction.

Although newer drugs such as cannabinoid receptor blocker[49,50] and dual action PPAR alpha / gamma agonist[51] are on the horizon, evidence is emerging that prescribing insulin sensitizers for their multiple anti-atherosclerotic effects may be indicated,[52-56] but clear guidelines from more studies are needed.[57] There are no studies yet demonstrating benefits for hard cardiovascular endpoints by the specific use of insulin sensitizers, though these are ongoing.[58,59] In the Proactive, Prospective Pioglitazone Clinical Trial in Macrovascular Events Study.[60] The procedural components in the primary endpoint of the trial made it difficult to show any significant statistical benefit but some effects were seen on secondary endpoints.[61,62] On a positive note, apart from weight gain there were no serious side effects noted during this study. But the weight gain worsened heart failure in those with failing hearts. As the reviewer Dr. Hannele YK Jarvinen pointed out,[62] the results may be good for patients who are not at risk for heart failure –with healthy arteries and with good heart function.

As part of the global CVD risk, short-term (10-year) CHD risks assessment by risk scores for TLC, anti-platelet and anti-lipid therapy initiation is well established. Newer noninvasive imaging for subclinical atherosclerosis is available but needs cost-effective guidelines for its role. Since chronic disease prevention is sidelined in many developing countries in spite of availability of viable and proven interventions,[63–65] the onus is on health care professionals for early detection and management of absolute risks. Clearly population-based strategies are more effective in the long term, and this is possible even without increased use of medications, as shown by the analysis of patterns of declining blood pressure in the WHO MONICA project.[66] This gives us hope for a reversal of epidemiological trends with Mets / IRS but the mechanisms are not evident yet. Till such time as we do that, population-based and absolute risk based interventions are relevant to CVD prevention in the 21st century.[67]

Conclusions

Hyperinsulinemia is contributory to the excess CVD risk in IR. A paradigm shift targeting insulin reduction to the levels seen in nondiabetic and non-CVD risk population in the community is necessary to counter the epidemic of T2 DM[68] and CVD.[69] High WC alone has significant sensitivity for diagnosing MetS / IRS. Whilst instituting therapeutic lifestyle changes, it may be prudent to do insulin levels or HOMA-IR or calculate insulin sensitivity index. There are practical difficulties in assaying and interpreting insulin levels. Use of an insulin sensitizer in MetS / IRS and pre-diabetic state is very likely to be beneficial where TLC is failing or likely to fail. Although PROactive study raises some doubts that glitazones could offer a solution for macrovascular disease, we must await the results of ongoing and future studies with a fair degree of optimism.

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