CLINICAL PRACTICE

The clinical relevance of fasting serum insulin levels in obese subjects

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In the past, the clinical relevance of serum insulin concentration has been minimal. Assessment of residual islet beta cell function in diabetics relies on the measurement of C-peptide rather than insulin. Measurement of insulin is clinically important only for the detection of insulinomas and rare genetic defects that lead to severe insulin resistance or defective insulin secretion. The major value of determining serum insulin levels is restricted to research studies investigating the aetiology of type 2 diabetes and the metabolic syndrome. However, in recent years pathology laboratories in South Africa and elsewhere have seen an increase in the number of requests for serum insulin measurements for the assessment of insulin resistance using the HOMA (homeostasis model assessment)[1] and QUICKI (quantitative insulin sensitivity check index)[2] formulae. These formulae use fasting insulin and glucose levels as a measure of insulin resistance. The gold standard for assessing insulin resistance is the euglycaemic, hyperinsulinaemic clamp method, a technique not suited for use in a GP or specialist practice. The HOMA and QUICKI methods are quicker, easier and cheaper to perform and give results that have been shown to correlate with data obtained from the clamp technique.[1,2]

Obesity and insulin resistance

The reason for the current trend of assessing insulin resistance using the HOMA and QUICKI formulae may be related to the high prevalence of obesity in South Africa[3] and the increasing demands made on physicians by patients who wish to lose weight. Unfortunately, the strong association between insulin resistance and obesity[4,5] has been misinterpreted by some health workers, who claim that insulin resistance causes obesity. Insulin resistance is in fact a direct effect, and not a cause, of obesity and is a physiological response to reduce further weight gain.[5] The main function of insulin within the adipocyte is to inhibit triglyceride breakdown (lipolysis) and therefore insulin resistance leads to increased lipolysis and a slowing down of triglyceride deposition within the adipocytes. This explains why insulin and sulphonylurea therapy lead to weight gain, as does treatment of type 2 diabetes with the thiazolidinedione families of insulin sensitisers.[6,7] However the biguanide, metformin, does not cause weight gain but rather may induce modest weight loss.[6] This seems to contradict the statement that increased insulin sensitivity can lead to increased weight gain. Recent studies, however, have shown that the mechanism of action of metformin may not be due entirely to its effects on insulin sensitivity. Rather, metformin increases glucose clearance in an insulin-independent fashion. Metformin acts by activating the intracellular enzyme adenosine monophosphate (AMP)-activated protein kinase (AMPK).[8] This enzyme increases glucose uptake in a similar fashion to insulin but independently of the hormone and also reduces lipid synthesis,[9] which may explain metformin's ability to induce some weight loss. Metformin has been used to treat obesity, but its effects have been modest.[10] A large clinical study[11] has shown that lifestyle intervention in conjunction with dietary modification is far more effective than metformin in preventing the onset of type 2 diabetes in obese subjects. Furthermore, metformin has undesirable side-effects, particularly gastro-intestinal effects and rarely lactic acidosis.[6]

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Aetiology of obesity-associated insulin resistance

How does obesity cause insulin resistance? Researchers and clinicians have been attempting to answer this question for many years, and the current opinion is that there are many factors involved in the aetiology of obesity-related insulin resistance. Primarily, the adipocyte is the source of a number of factors that have been shown to effect insulin sensitivity. These factors include free fatty acids, tumour necrosis factor alpha, interleukin 6 and adiponectin.[12] In addition, triglyceride deposition within the muscle is increased in obese subjects and the level of intramyocellular triglyceride has been shown to correlate negatively with insulin sensitivity.[13] Thus, there are numerous clinical and *in vitro* studies demonstrating the ability

of adipose tissue to increase insulin resistance. Furthermore obesity, via its ability to increase insulin resistance, is thought to play a prime role in the aetiology of the metabolic syndrome. This disorder is characterised by dyslipidaemia, glucose intolerance, insulin resistance, hypertension and abdominal obesity.[14] However, the latest guidelines published by the National Cholesterol Education Program (NCEP) for the diagnosis of this syndrome recommend that insulin resistance be assessed using fasting plasma glucose rather than fasting serum insulin levels.[15] This highlights the lack of clinical data supporting the use of HOMA, QUICKI or insulin levels for defining insulin resistance.

Diagnosis and treatment of insulin resistance

The measurement of insulin levels in obese subjects therefore seems to have little clinical relevance. As already noted, treating insulin resistance will not cause weight loss. Furthermore, there exists no clinical or biochemical definition of what constitutes an abnormal degree of insulin resistance. Therefore, it is not known at what level of HOMA, QUICKI or fasting insulin disease aetiology begins. A number of studies have measured insulin resistance in the general population and then defined cut-off points for the diagnosis of insulin resistance. The cut-off points defined in these studies were the 25th centile of insulin sensitivity[16,17] and the lower limit of the 95% confidence intervals for the QUICKI.[18] These studies each used a different method for measuring insulin sensitivity/resistance and a different population group. These cut-off points are therefore not universally applicable. Furthermore, there is the question of what treatment should be used in the case of insulin-resistant subjects. The biguanides and thiazolidinediones are indicated for diabetic subjects only, and all cause weight gain (with the exception of metformin). Polycystic ovary disease (PCOS) is associated with increased insulin resistance, but not necessarily obesity, and studies have shown that treatment with insulin sensitisers does improve fertility.[19] This suggests that some disorders other than type 2 diabetes can be treated with insulin sensitisers. However, in the case of the metabolic syndrome the best method for improving insulin sensitivity remains weight loss. It has been shown that even a modest loss in weight of 5 - 10% of current body mass can have clinically significant effects on fasting insulin, glucose and lipid levels as well as blood pressure.[20] Therefore, a safe and effective alternative to the use of insulin sensitisers is readily available. Unfortunately, long-term adherence to lifestyle changes and diets is very difficult, often requiring considerable input from a health care professional and total commitment from the patient. This may explain why the preferred method of treatment is the 'magic' pill.

In conclusion, the measurement of insulin resistance in obese subjects is not warranted. The co-morbid diseases associated with obesity may rely on the presence of insulin resistance,[14] but the insulin resistance is a result rather than a cause of high body fat mass.[5] Weight loss has clearly been shown to have favourable effects on the metabolic dysfunction associated with obesity[20] and therefore it is the adiposity that should be the prime target for both clinician and patient rather than the insulin resistance.

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IN BRIEF

Irritable bowel syndrome

Irritable bowel syndrome (IBS) is a cluster of symptoms without a recognised aetiopathology, but in which a variety of different biological, psychological, and social factors can be implicated. Identification of meaningful subgroups of patients within the syndrome is important as these groups may represent different aetiological and pathophysiological entities, and they may require different treatment approaches. Using the gastro-intestinal symptoms together with rectal sensitivity and psychological symptoms, researchers aimed to identify subgroups of IBS sufferers. They surmised that such groupings, which cross conventional diagnostic approaches, might provide greater understanding of the pathogenesis of the condition. They grouped 107 clinic patients with IBS according to physiological, physical and psychological parameters. All patients had severe IBS and had failed to respond to usual medical treatment. Of the 107, 29 had predominantly diarrhoea and 26 predominantly constipation, while 52 had alternating bowel habits.

Three subgroups were identified: Group I comprised patients with low distension thresholds and high rates of psychiatric morbidity, doctor consultations, interpersonal problems, and sexual abuse. Group II also had low distension thresholds, but low rates of childhood abuse and moderate levels of psychiatric disorders. Group III had high distension thresholds, constipation or alternating IBS, and low rates of medical consultations and sexual abuse.

The report of the study in *Gut* (2003; **52:** 1616-1622) concluded that the marked differences across the three groups suggest that each may have a different pathogenesis and may respond to different treatment. Inclusion of psychosocial factors in the analysis enabled more clinically meaningful groups to be identified than those traditionally determined by bowel symptoms alone or together with rectal threshold.