Insulin levels in insulin resistance: phantom of the metabolic opera?

Katherine Samaras, Aidan McElduff, Stephen M Twigg, Joseph Proietto, John B Prins, Timothy A Welborn, Paul Zimmet, Donald J Chisholm and Lesley V Campbell

ABSTRACT

- Insulin resistance is considered a core component in the pathophysiology of the metabolic syndrome.
- Some clinicians measure serum insulin concentrations in the mistaken belief that they can be used to diagnose insulin resistance.
- Serum insulin levels are poor measures of insulin resistance. Furthermore, there is no clinical benefit in measuring insulin resistance in clinical practice.
- Measurements of fasting serum insulin levels should be reserved for large population-based epidemiological studies, where they can provide valuable data on the relationship of insulin sensitivity to risk factors for diabetes and cardiovascular disease.
- Clinicians should shift from identifying "insulin resistance" to identifying risk factors, such as fasting glucose and lipid levels, hypertension and central obesity. These proven risk factors converge within the metabolic syndrome.
- Individuals "at risk" of diabetes and atherosclerotic cardiac disease can be identified simply and inexpensively, using classic clinical techniques, such as history-taking, physical examination, and very basic investigations.

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Obesity and related components of the metabolic syndrome are the greatest future public health threats, as precursors of cardiovascular disease (CVD)[1] — the leading cause of death in the developed world. They also precede diabetes, which accelerates CVD and has its own specific complications (eg, renal failure). The obesity epidemic may undo the success of health strategies for CVD reduction (namely, improved nutrition and smoking cessation) and proven therapies such as antilipid therapy and aspirin. Although this epidemic is most obvious in the industrialised world, similar trends are evident in the developing world.[2] Understandably, the medical profession is concerned with early identification of people at risk of CVD and diabetes, in the hope of prevention. Conceptually, identifying the metabolic (or insulin resistance) syndrome identifies risk for CVD or diabetes.

In this article, we explain how, historically, insulin resistance brought together facets of the metabolic syndrome and the pathogenesis of diabetes and atheroma, but has since been clinically "overtaken" by central obesity, now accepted as the core component of the metabolic syndrome. Further, we argue that the measurement of serum insulin levels to diagnose insulin resistance, while a valuable research tool, has no place in current clinical practice.

Why identify the metabolic syndrome?

The metabolic syndrome encompasses a wide range of metabolic disturbances in glucose, insulin and lipid metabolism, and is associated with central abdominal obesity.[1] A recent Australian mortality study showed that waist–hip ratio is a better predictor of CVD mortality than fasting serum cholesterol level is.[3] The presence of the metabolic syndrome doubled the risk of death from coronary disease in the Second National Health and Nutrition Examination Survey, after adjustment for age, sex, cholesterol level, physical activity, and smoking.[4] In the Kuopio Ischaemic Heart Disease Risk Factor Study, non-diabetic Finnish men with the metabolic syndrome were three times more likely to die from coronary disease than men without, after adjusting for age, low-density lipoprotein cholesterol level, smoking, and family history.[5] These observations suggest treating traditional cardiac risk factors will not fully eliminate the increased cardiovascular risk in individuals with the metabolic syndrome.

The Adult Treatment Panel III guidelines recommend targeted identification of individuals with the metabolic syndrome[6] — clearly prudent clinical practice. However, there are no specific studies that show any benefit in identifying the metabolic syndrome rather than treating its individual major components. Further, the definition of the metabolic syndrome has been an area of controversy, with multiple overlapping definitions. Most recently, the International Diabetes Federation (IDF) developed a simple clinical tool to define the metabolic syndrome, which will identify individuals at highest risk for CVD and type 2 diabetes: it involves central obesity, diabetes, dyslipidaemia, and hypertension.[7] Before the IDF definition, the most widely used classifications (those of the World Health Organization[8] and the Adult Treatment Panel III[6]) referred to insulin resistance as a pivotal component. These and other classifications have led to considerable confusion in the clinical setting, and when attempting to compare the burden of the metabolic syndrome between populations.[7] As a result, the IDF identified a need to rationalise the variety of definitions.[7] In their "definitive definition", no measure of insulin resistance is included — instead, central obesity has effectively replaced insulin resistance.

Why does insulin resistance matter?

Insulin resistance refers to reduced insulin-stimulated glucose uptake in skeletal muscle and impaired suppression of endogenous glucose production, which are critical for maintaining normal glucose homeostasis. Insulin resistance is partly explained by genetic factors, with genetic sharing between the metabolic syndrome phenotypes of insulin resistance and abdominal fat.[9] Insulin resistance may be the earliest identifier of subsequent CVD risk; it is established as an early diabetes risk factor, and it is fundamentally entwined among the pathophysiological aberrations of the metabolic syndrome. It is present in type 2 diabetes, central obesity, atherosclerotic CVD, most dyslipidaemias, and polycystic ovary syndrome. However, although insulin resistance is present, so are many metabolic co-conspirators — disturbances in lipid metabolism, increasingly elaborate networks of proinflam-

matory cytokines and adipokines, and environmental factors, such as sedentary lifestyle and smoking. Research has not yet yielded a singular culprit for these conditions, but reveals a complex and disturbed physiology acting to the detriment of the person.[1]

Why not to measure insulin resistance

Insulin resistance is elusive, perhaps more easily identified than measurable. The WHO classification of the metabolic syndrome includes insulin resistance, but only when measured by hyperinsulinaemic euglycaemic clamp with comparison to normative background population ranges. People in the lowest quartile are defined as having insulin resistance. Thus, the a priori chance of finding insulin resistance is (at least) one in four. The clamp requires bilateral cannulation, arterialisation of blood flow to the vein, 2 hours of measures, and experience. The clamp may be practical for research conducted in large facilities, but clearly is not appropriate in clinical practice. Obtaining normative sex- and ethnic-specific population data for comparison is another difficulty. Simpler alternative estimates have evolved in clinical research, especially for large studies where the clamp is deemed impractical or too costly. In our view, these alternative estimates remain a research tool only. Unfortunately, patients are being referred to us after some of these measures, such as fasting serum insulin level, have been assayed — with no data supporting their diagnostic or prognostic value, and with no useful intervention available.

We believe a litany of fundamental problems exists with the measurement of fasting serum insulin level. Fasting serum insulin level or (worse still) insulin responses during an oral glucose tolerance test seem to be used, by some practitioners, to "diagnose" or "measure" insulin resistance, without normal or appropriate reference ranges or any scientific evidence of clinical utility. We recall the painstaking evidence drive for cholesterol measurement and therapy in health and disease, with outcome-related ranges. No similar evidence exists for fasting serum insulin level.

Prospective mortality studies have shown insulin measures do not predict cardiovascular mortality when metabolic syndrome characteristics, such as lipids, are taken into account.[10] Furthermore, the relationship between clamp insulin resistance and fasting serum insulin level is weak: fasting serum insulin level explains only 36% of variance in insulin resistance,[11] even less when glucose metabolism is impaired.[11] Measurement of serum insulin levels has been described as "fraught with errors and inconsistencies";[12] a clinician who ordered this inappropriate test would be overwhelmed by poor 120-minute reproducibility, among other problems.[13] By analogy, fasting serum insulin level is a capricious little beast subject to intra-individual variation on any couple of days, and substantial inter-assay and inter-laboratory variations; interpreting fasting serum insulin levels may be considered like wrestling a column of smoke.

We understand insulin responses to an oral glucose tolerance test to be more a test of insulin secretion rather than resistance (and even then of low validity). A vigorous insulin response during an oral glucose tolerance test reflects gastric emptying and beta-cell insulin secretion, more than insulin action. A flat insulin response in a patient with insulin resistance may indicate a beta-cell secretory deficit.

Measurement aside, reference ranges for normal subjects present another problem: do they exist? There are few studies reporting fasting insulin in "normals" (normal being a control or, at best, "non-obese").[13] There are no normal reference ranges in healthy weight, healthy-waisted subjects with no symptoms or signs of polycystic ovary syndrome or hyperandrogenism, and no first-degree family members with type 2 diabetes.

The scientific argument is against measurement of fasting or stimulated serum insulin levels in any clinical practice setting.

In light of the evidence, we believe fasting serum insulin measurements should be reserved for large population-based epidemiological studies, where they can provide valuable data on the relationship of insulin sensitivity to risk factors for diabetes and cardiovascular disease.

Why does this debate matter?

What of the patient "diagnosed" with insulin resistance using serum insulin levels? What are the implications for other matters, such as obtaining employment or qualifying for life or health insurance? Will the lowest 25% of an otherwise healthy population be an attractive target for the pharmaceutical industry? We know of at least two large trials examining pharmacological agents in type 2 diabetes prevention in very high-risk groups. If these trials are successful, as was metformin in the Diabetes Prevention Program,[14] will we be able to resist the temptation to extend these measures to all "insulin resistant" patients? In a world of consumer advocacy, might patients, fearing the "insulin resistance" juggernaut, demand treatment? We are already concerned that otherwise well patients whom we see in practice are demanding (and receiving) metformin, or are being told they need it, particularly for polycystic ovary syndrome.

Are there better ways of identifying future ill health from CVD or diabetes? In our opinion, certainly — easily, quickly and cheaply. We proffer classic, time-honoured, and recently neglected skills: history-taking and physical examination. These should cover presence of central obesity, difficulties in weight management, menstrual irregularity, acne and hirsutism, lipid disturbances, atheroma, hypertension, gestational diabetes, and family history of diseases such as type 2 diabetes and CVD. Furthermore, history-taking and physical examination identify factors (ie, hypertension, obesity, and dyslipidaemia) for which irrefutable evidence of treatment benefit exists.

In the meantime, we await evidence of benefit from those clinicians promulgating measurement of fasting serum insulin levels in clinical practice. We are doubtful such evidence can ever be presented.

Competing interests

None identified.

Author details

Katherine Samaras, MB BS, PhD, FRACP, Postdoctoral Research Fellow and Endocrinologist[1,2]
Aidan McElduff, MB BS, PhD, FRACP, Staff Endocrinologist[3]
Stephen M Twigg, MB BS, PhD, FRACP, Endocrinologist and Clinical Academic[4]
Joseph Proietto, MB BS, PhD, FRACP, Staff Endocrinologist[5]
John B Prins, MB BS, PhD, FRACP, Staff Endocrinologist[6]
Timothy A Welborn, MB BS, PhD, FRACP, Endocrinologist[7]
Paul Zimmet, AO, MB BS, MD, FRACP, Director[8]
Donald J Chisholm, MB BS, MRACP, FRACP, Staff Endocrinologist[1,2]
Lesley V Campbell, MRCP, FRCP, FRACP, Staff Endocrinologist,[1,2]

1 Diabetes and Obesity Program, Garvan Institute of Medical Research, Sydney, NSW.
2 Department of Endocrinology, St Vincent's Hospital, Sydney, NSW.
3 Department of Endocrinology, Royal North Shore Hospital, Sydney, NSW.
4 Discipline of Medicine, University of Sydney, Sydney, NSW.
5 Department of Medicine, Austin Health, Melbourne, VIC.
6 Centre for Diabetes and Endocrine Research, University of Queensland, Brisbane, QLD.
7 Department of Endocrinology and Diabetes, Sir Charles Gairdner Hospital, Perth, WA.
8 International Diabetes Institute, Melbourne, VIC.
Correspondence: k.samaras@garvan.org.au

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