Fortnightly Review

Insulin resistance

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During the past 20 years it has become clear that the clinical implications of insulin resistance reach far beyond that of the rare diabetic patient requiring excessive quantities of exogenous insulin. Today the potential ramifications of impaired insulin action are recognised by clinicians ranging from endocrinologists to cardiologists. Central to this expanding interest is Gerald Reaven's hypothesis that tissue resistance to the effects of insulin is a factor linking non-insulin dependent diabetes mellitus, essential hypertension, and coronary heart disease. These three diseases together are responsible for substantial (and increasing) morbidity and premature mortality worldwide.¹ However, much uncertainty remains about the association between insulin resistance and human disease.² For example, although relative hyperinsulinaemia and other features of the insulin resistance syndrome can be identified in a proportion of apparently healthy individuals,³ the prevalence of insulin resistance is unknown. This is because of the difficulties of defining insulin resistance in clinical terms and of quantifying insulin action in humans.

Methods

I selected the articles cited in this review according to their scientific impact and clarity of presentation. The emphasis is on studies which are of relevance to insulin action in humans. Review articles, generally by authors with established reputations and published in high quality scientific journals, have been supplemented by original papers that include important recent developments. The review also reflects a decade of personal clinical and research interest in insulin resistance.

Assessment of insulin action

CLINICAL FEATURES

In practice insulin resistance is usually inferred from the presence of features such as obesity. Other signs suggestive of pathological insulin resistance include the hyperkeratotic condition acanthosis nigricans (fig 1) and, in women, ovarian hyperandrogenism.³ Rarely, acral hypertrophy and other acromegaloïd features (with normal growth hormone concentrations) are found. Precocious pseudopuberty, growth retardation, lipodystrophy, and hyperlipidaemia are also recognised. Glucose tolerance may be normal or impaired—diabetes develops only when compensatory insulin secretion fails.

TECHNIQUES FOR QUANTIFYING INSULIN ACTION IN HUMANS

Insulin resistance may be defined in pharmacological terms as a state in which normal amounts of insulin produce a subnormal biological response.⁴ Since islet B cell dysfunction may coexist with impaired insulin action^{5,6} normoglycaemic or hyperglycaemic patients with hyperinsulinaemia require more rigorous evalua-

tion. Several investigative techniques have been devised, but all have limitations and none is suitable for routine clinical use.⁷

The hyperinsulinaemic euglycaemic clamp, which involves simultaneous infusions of insulin and glucose, has been used extensively and is widely regarded as the standard. Briefly, if endogenous hepatic glucose production is completely inhibited by an intravenous infusion of insulin then the quantity of exogenous glucose required to maintain euglycaemia (the M value) is a reflection of the net sensitivity of target tissues (mainly skeletal muscle) to insulin (fig 2). Infusions at different plasma insulin concentrations allow construction of whole body dose-response curves.

Enthusiastic application of the glucose clamp technique has tended to diminish the concept of insulin resistance to a reduced M value.⁷ This value reflects the sustained hyperinsulinaemia attained in most clamps which is inappropriate for assessing other key aspects of intermediary metabolism. Adipocyte lipolysis, for example, is maximally regulated at low physiological plasma concentrations of insulin (box 1).⁵

Physiological states of insulin resistance

The imperfect definition of insulin resistance limits its clinical use.^{4,8} Insulin sensitivity spans a broad range (threefold to fourfold) even among apparently healthy people with normal glucose tolerance.¹ Many inherited and acquired factors can affect insulin sensitivity.⁹ Some of these, sex for example, are immutable. However, associated factors such as regional adiposity, skeletal muscle mass, and level of physical conditioning are

Fig 2—Mean (SE) plasma immunoreactive insulin concentrations (A) and tissue glucose uptake (B) for subjects with normal glucose tolerance, impaired glucose tolerance, and non-insulin dependent diabetes mellitus as determined during euglycaemic hyperinsulinaemic clamps. Reproduced from "J Clin Invest" 1981;68:957-69 with permission

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Fig 1—Acanthosis nigricans (cutaneous marker of insulin resistance) in axilla of young woman with glucose intolerance and hyperinsulinaemia

Box 1—Regulatory effects of insulin on key aspects of metabolism

Action	Plasma insulin range for maximal effect
Inhibition of adipocyte lipolysis	Low physiological
Inhibition of hepatic glucose production	Low physiological
Stimulation of tissue glucose uptake	High physiological
Transmembrane ion transport	Pharmacological

For endogenously secreted insulin portal blood concentrations are about twofold higher, reflecting hepatic clearance.

The anabolic actions of insulin also include stimulation of lipogenesis and tissue amino acid uptake.

potentially modifiable. Hormonal changes associated with puberty and pregnancy (second and third trimesters) often lead to substantial increases in insulin requirements.^{10 11} The effect of aging on insulin sensitivity is disputed.¹²

Conditions associated with insulin resistance

Insulin resistance occurs in many aetiologically diverse human disorders (boxes 2 and 3). In the extreme insulin resistance syndromes (box 3) resistance is an important determinant of the clinical phenotype. In other conditions—for example, impaired glucose tolerance, non-insulin dependent diabetes—the degree of tissue insulin resistance is less. A pathological role for

Box 2—Pathological conditions associated with insulin resistance in humans**Acquired conditions**

Antagonism of insulin action:
Acute counterregulatory hormone excess (trauma, severe sepsis, acute myocardial infarction, diabetic ketoacidosis—common)
Certain drugs (corticosteroids, β blockers—common)
Thyrotoxicosis (common)
Polycystic ovary syndrome (relatively common)
Acromegaly (rare)
Pheochromocytoma (rare)
Cushing's syndrome (rare)
Insulinoma (rare)
Glucagonoma syndrome (very rare)
Cardiological syndromes:
Congestive cardiac failure (common)
Atheromatous disease (common)
Microvascular angina (uncommon)
Other major organ failure (relatively common):
Hepatic cirrhosis
Chronic renal failure
Inherited (all uncommon or rare)
Myotonic dystrophy
Prader-Willi syndrome
Alström's syndrome
Laurence-Moon-Biedl syndrome
Werner's syndrome
Friedreich's ataxia

Box 3—Syndromes associated with extreme insulin resistance

Insulin receptor mutations:

Leprechaunism

Rabson-Mendenhall syndrome

Type A insulin resistance (mutations are relatively uncommon)

Post-binding defects in insulin action:

Lipodystrophic diabetes syndromes (includes inherited and acquired forms)

Type C insulin resistance (post-receptor defect; overlaps with type A)

Insulin receptor antibodies:

Type B insulin resistance (usually associated with evidence of other autoimmune disease)

All of these syndromes are uncommon or rare. Glucose tolerance may be only minimally impaired if compensatory hyperinsulinaemia is sufficient to overcome the defect.

insulin resistance has been proposed in conditions as disparate as myotonic dystrophy,⁵ chronic renal failure, and hepatic cirrhosis. However, in many other disorders the clinical significance of impaired insulin action, if any, is uncertain.

OBESITY

Development of obesity is associated with acquired insulin resistance. Compensatory hyperinsulinaemia in obese patients reduces the expression of the membrane insulin receptor (down regulation). This is associated with a rightward shift in the glucose uptake dose-response curve with preservation of the maximal response.¹³ Post-receptor defects reduce maximal responses. The distribution of adipose tissue also affects insulin action¹⁴; upper body (android) obesity and, in particular, visceral fat deposition (indicated by a high waist:hip ratio) is more closely associated with glucose intolerance and other features of the insulin resistance syndrome (box 4) than lower body (gynaecoid) obesity.^{9 14} Certain populations with a high prevalence of non-insulin dependent diabetes (for example, Pima Indians, Mexican Americans, South Asians) are predisposed to abdominal obesity.

The recent cloning of the ob gene and the isolation of its product—leptin—has provided new insights into the relation between obesity and insulin resistance. Alterations in the production of, or sensitivity to, leptin cause obesity and diabetes in rodents. In humans, insulin resistance is associated with raised plasma leptin concentrations independent of body fat mass. A causal relation between leptin and insulin sensitivity has been suggested, and this may help explain the pathogenesis of the insulin resistance syndrome.^{15 16}

IMPAIRED GLUCOSE TOLERANCE

Impaired glucose tolerance is defined as hyperglycaemia during an oral glucose tolerance test which is insufficient for the diagnosis of diabetes mellitus. Although a heterogeneous syndrome, impaired glucose tolerance is often a transition stage in the progression from normal glucose tolerance to non-insulin dependent diabetes. Glucose clamp studies have shown a rightward shift in insulin stimulated disposal of glucose with preservation of maximal effects at pharmacological insulin concentrations.¹³ Abnormalities of other aspects of intermediary metabolism and B cell function have also been shown.^{3 6 17}

**Box 4—The insulin resistance syndrome
Reaven's syndrome (syndrome X)**

Resistance to insulin stimulated glucose uptake
Glucose intolerance
Hyperinsulinaemia
Increased very low density lipoprotein triglyceride concentration
Decreased high density lipoprotein cholesterol concentration
Hypertension
Associated metabolic abnormalities
Small dense low density lipoprotein cholesterol particles
Hyperuricaemia
Raised plasminogen activator inhibitor 1 concentrations

NON-INSULIN DEPENDENT DIABETES MELLITUS

In established non-insulin dependent diabetes the insulin mediated suppression of hepatic glucose production (the principal determinant of fasting plasma glucose concentration) and tissue glucose uptake are impaired.^{2,9,17} Uncertainty about the relative importance of these defects¹⁸ partly reflects methodological problems.¹⁹ Since hepatic glucose production is inhibited at low physiological insulin concentrations the high plasma concentrations attained in clamp studies tend to favour identification of defects in glucose uptake (box 1). Glucose clamp studies in patients with non-insulin dependent diabetes show a defect in insulin action at a site(s) distal to the binding of insulin to its membrane receptor. Defects in intracellular oxidation and storage of glucose (as glycogen) have been identified.^{2,9,17} However, it remains unclear whether insulin resistance is a primary cause of non-insulin dependent diabetes or whether a genetically determined failure of insulin secretion is unmasked.^{9,20} Insulin resistance is not a prerequisite for the development of non-insulin dependent diabetes. In maturity-onset diabetes of the young some affected families have mutations of the glucokinase gene which result in impaired B cell function and fasting hyperglycaemia.²¹

Other potential modulating factors merit consideration. For example, in one recent study of the common adult phenotype of non-insulin dependent diabetes insulin resistance was largely confined to patients with microalbuminuria or hypertension.²² In non-obese black patients with non-insulin dependent diabetes, insulin resistant and sensitive subgroups have been identified, with abdominal fat deposits correlating with insulin resistance only in the resistant group.²³

REAVEN'S SYNDROME (SYNDROME X)

In 1988, Gerald Reaven of Stanford University brought together several strands of experimental and epidemiological evidence postulating that resistance to insulin mediated glucose uptake and hyperinsulinaemia affect the development and clinical course of three major related diseases—non-insulin dependent diabetes mellitus, essential hypertension, and coronary artery disease.¹ Reaven drew attention to the clustering of key metabolic abnormalities—all risk factors for coronary artery disease—in certain groups of subjects (box 4), calling the assembly syndrome X.¹ This term had already been used to denote angina pectoris in association with reversible electrocardiographic ischaemia and angiographically normal coronary arteries (microvascular angina). Subsequently, a degree of overlap between the metabolic and cardiological syndromes

has been reported.²⁴ Other cardiovascular risk factors have been identified which are also components of syndrome X (box 4).

The nature of the postulated association between insulin resistance and coronary artery disease remains obscure. Reaven has argued that tissue insulin resistance is the primary initiating defect which leads to compensatory hyperinsulinaemia and atherogenic risk factors.^{1,24} Hyperinsulinaemia has been shown, with some inconsistencies, to be associated with coronary artery disease in cross sectional and prospective population based studies.^{8,25} The inconsistencies may partly reflect the clustering of risk factors in individuals with the insulin resistance syndrome.²⁶ Experimental evidence that insulin stimulates proliferation of smooth muscle cells and augments lipid synthesis in vascular smooth muscle cells has provided further theoretical links between insulin and atherogenesis.²⁷ However, the clinical relevance of these observations is disputed, and the association between insulin and atherosclerosis remains controversial.^{28,29}

Insulin resistance is implicated in the pathogenesis of accelerated atherosclerosis in subjects with non-insulin dependent diabetes³⁰ and impaired glucose tolerance. It has been suggested that the high incidence of coronary heart disease among emigrants from the Indian subcontinent, which appears to be associated with insulin resistance, might be reduced through lifestyle changes.³¹

Patients with essential hypertension often have exaggerated responses of plasma glucose and insulin to an oral glucose challenge.^{32,33} This may be due to activation of the sympathetic nervous system, diminished adrenomedullary activity, or enhanced renal sodium retention by hyperinsulinaemia.³⁴ In addition, subjects with hypertension tend to have higher plasma triglyceride and lower high density lipoprotein cholesterol concentrations. Ethnicity seems to be important in the relation between blood pressure and insulin sensitivity; differences have been observed between whites, blacks, and Pima Indians.^{32,33} Insulin resistance in peripheral tissues has been shown in hypertensive subjects^{34,35} as well as in normotensive first degree relatives of white European hypertensive subjects.³⁶ Non-endocrine secondary forms of hypertension do not seem to be associated with insulin resistance.

Molecular mechanisms of insulin resistance**INHERITED DEFECTS**

Rare mutations of the insulin receptor gene are the best characterised causes of insulin resistance that have been identified to date.^{37,38} Impairment of intrinsic tyrosine kinase activity in the insulin receptor has been reported not only in patients with non-insulin dependent diabetes³⁷ but also in non-obese normoglycaemic patients with insulin resistance. Type A insulin resistance, some cases of which are due to insulin receptor mutations, shares some metabolic and clinical features with the more prevalent polycystic ovary syndrome. This syndrome is characterised by a less severe post-binding defect in insulin action in which the effects of raised plasma androgen concentrations are compounded by low concentrations of sex hormone binding globulin. Though the relation between insulin resistance, hyperinsulinaemia, and ovarian androgen secretion remains unclear, recent evidence indicates that treatment with metformin reduces plasma insulin concentrations and ameliorates hyperandrogenism.³⁹

Lipodystrophic diabetes comprises a heterogeneous group of uncommon inherited or acquired disorders which may be associated with severe insulin resistance (fig 3). The molecular basis of these conditions remains elusive.³⁷ Hyperlipidaemia and hepatic cirrhosis are among recognised associations of some forms.

Fig 3—Acquired, generalised lipodystrophy in a patient with non-insulin dependent diabetes and combined hyperlipidaemia

ACQUIRED FORMS OF INSULIN RESISTANCE

Raised concentrations of circulating hormones which antagonise the metabolic actions of insulin (glucagon, cortisol, catecholamines, and growth hormone) are associated with impaired insulin action. These hormones, acting mainly at post-binding sites, contribute to the acute insulin resistance associated with diabetic ketoacidosis, severe sepsis, or major trauma. Specific hypersecretory endocrinopathies (box 2) are often associated with glucose intolerance or, less commonly, diabetes. By contrast, hypopituitarism and hypoadrenalism⁴⁰ are associated with increased tissue insulin sensitivity.

Insulin resistance may also result from treatment with corticosteroids (dose dependent effect), β -adrenergic blockers (especially drugs without intrinsic β_2 -agonist activity),³³ and thiazides at higher doses.⁴¹ Non-randomised studies suggest that these drugs may promote the development of non-insulin dependent diabetes mellitus in predisposed people.⁴² The failure of these drugs to produce the predicted reduction in incidence of coronary heart disease in hypertensive patients has led to speculation that adverse metabolic effects may have attenuated the anticipated benefits.^{33, 34} By contrast, the angiotensin converting enzyme inhibitor captopril and the α -adrenergic blockers prazosin and doxazosin reportedly improve insulin mediated glucose uptake.⁴³ However, the design and interpretation of some studies has been criticised and the therapeutic implications of these observations remain unclear.

Reduction of blood pressure does not necessarily improve defects in insulin action³³; nephropathy (which is associated with insulin resistance)²² is the main indication for angiotensin converting enzyme inhibitors in diabetic patients. A further consideration is the suggested decrease in muscle capillary density and reduced insulin stimulated vasodilatory response in skeletal muscle in subjects with insulin resistance.^{9, 44}

Raised blood glucose concentrations, possibly resulting in overactivity of the hexosamine pathway, may aggravate tissue insulin resistance and defective B cell function in non-insulin dependent diabetes.^{45, 46} In addition, raised plasma concentrations of non-esterified fatty acids, which are another feature of non-insulin-dependent diabetes, antagonise the uptake and oxidation of glucose in skeletal muscle through the glucose-fatty acid cycle⁴⁷; gluconeogenesis is also accelerated, exacerbating the hyperglycaemia. Raised fatty acid concentrations may also contribute to hypertriglyceridaemia.

ADDITIONAL POTENTIAL MECHANISMS

A mutation of the β_3 -adrenergic receptor has been reported to be associated with features of the insulin resistance syndrome, although its importance has been questioned.⁴⁸ The roles of defective function of the insulin sensitive glucose transporter protein (glut 4), abnormal endogenous insulin pulsatility,² and activities of key enzymes in tissue glucose metabolism remain unclear. The contribution of interference with intracellular post-binding phosphorylation cascades by adipocyte tumour necrosis factor α in human insulin resistance is also uncertain.⁴⁹ Investigations continue into David Barker's fetal origins hypothesis.⁵⁰

Treatment of insulin resistance

The metabolic defects associated with some acquired forms of insulin resistance (such as simple obesity) are potentially fully reversible. However, the intrinsic inherited component associated with disorders such as non-insulin dependent diabetes, which is inherited as a complex trait,⁵¹ seems to be only partially reversible.

NON-PHARMACOLOGICAL MEASURES

Most subjects who are overweight or obese are able to maintain normal glucose tolerance by increasing endogenous insulin secretion. Nevertheless, excess adipos-

Summary points

- Insulin resistance is a state in which normal concentrations of insulin produce a subnormal biological response
- Patients with insulin resistance have hyperinsulinaemia together with normoglycaemia or hyperglycaemia
- Insulin resistance is commonly associated with obesity, non-insulin dependent diabetes mellitus, and essential hypertension
- The insulin resistance syndrome includes impaired insulin stimulated glucose uptake, hyperinsulinaemia, glucose intolerance, hypertension, and dyslipidaemia
- Drugs such as corticosteroids, β blockers, and high dose thiazides can exacerbate insulin resistance; angiotensin converting enzyme inhibitors and α blockers may reduce resistance
- Reducing insulin resistance is important in managing non-insulin dependent diabetes—for example, by losing weight, aerobic exercise, and stopping smoking; moderate alcohol consumption improves insulin resistance
- Metformin improves multiple aspects of the insulin resistance syndrome. Novel insulin action enhancing drugs including the thiazolidinediones are under evaluation

ity contributes to insulin resistance in most subjects with glucose intolerance or non-insulin dependent diabetes.^{9, 15} Obesity therefore represents an important modifiable component of the metabolic disturbance. In addition to total energy intake there is evidence that dietary fat composition may have an independent effect on insulin sensitivity.⁵² Unfortunately, weight reducing strategies usually require major changes in lifestyle which only a few obese patients are able to adopt and sustain.⁵³

Aerobic exercise of sufficient intensity and duration has beneficial effects on insulin sensitivity.⁵⁴ However, many subjects with non-insulin dependent diabetes are unable to participate in exercise programmes because of coexisting obesity, advanced age, or infirmity. Data from non-randomised studies suggest that regular physical exercise reduces the risk of developing non-insulin-dependent diabetes. Smoking is also associated with insulin resistance.²⁴ In a recent non-randomised prospective study of healthy middle aged American men cigarette smoking emerged as an independent risk factor for non-insulin dependent diabetes.⁵⁵ By contrast, moderate alcohol consumption was associated with a reduced risk of developing diabetes, possibly reflecting effects on insulin sensitivity.⁵⁶

DRUG TREATMENT

In diabetic subjects, reducing hyperglycaemia by either non-pharmacological measures or giving sulphonylureas, acarbose, or insulin may improve insulin action by lessening the toxic effects of glucose.^{9, 45} The only oral drug available in Britain and the United States with specific effects on insulin action in tissues is metformin.^{57, 58} Metformin is indicated primarily for overweight or obese subjects with non-insulin dependent diabetes in whom dietary measures have proved inadequate. During treatment plasma insulin concentrations fall while insulin stimulated glucose uptake is enhanced and hepatic glucose production is reduced.^{53, 57-59} Metformin also improves certain aspects of the insulin resistance syndrome in non-diabetic subjects.⁶⁰

Troglitazone is a member of a new class of orally active insulin sensitising drugs, the thiazolidinediones, which reduce plasma glucose, insulin, non-esterified

fatty acid, and triglyceride concentrations.^{61 62} Preliminary data suggest that the antihyperglycaemic effect of troglitazone is comparable with that of other oral antidiabetic drugs. Reports of beneficial effects on blood pressure in obese subjects await further confirmation.⁶¹ Troglitazone is likely to be licensed in Britain in the near future.

The roles of lifestyle changes and insulin sensitising drugs in preventing non-insulin dependent diabetes remain to be determined.⁶³ Randomised clinical trials are in progress. To date, treatments designed to reduce release or oxidation of non-esterified fatty acids have produced inconsistent results; toxicity has also been a problem with some drugs.⁶⁴ Fibric acid derivatives, indicated primarily for dyslipidaemias, may produce minor improvements in glycaemia. Other experimental therapies include β_3 -agonists,⁶⁴ recombinant human insulin-like growth factor-1,⁶⁵ and antibodies to tumour necrosis factor α and to the extracellular domain of the insulin receptor.⁶⁶ However, limited or uncertain efficacy or adverse effects are likely to restrict their use. An association between pulmonary hypertension and fenfluramine derivatives has recently focused attention on the risks and benefits of appetite suppressants.^{64 67} The withdrawal of the biguanide phenformin in many countries during the 1970s due to an unacceptable risk of lactic acidosis serves as a reminder of the necessity for rigorous evaluation of new drugs.⁵⁸

Conflict of interest: None.

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