Ten key facts on insulin resistance

Michael Mead

Introduction

To improve diabetes care for our population, primary care must have a fundamental understanding of the role of insulin resistance in the pathogenesis of diabetes and in producing the increased risk of cardiovascular disease. In this article I summarise what a primary care professional needs to know to enable the effective targeting of insulin resistance in their daily surgeries.

Insulin resistance is a fundamental cause of type 2 diabetes: 92% of people with type 2 diabetes have insulin resistance (Haffner, 1999) and it has been suggested that this develops 20–30 years before the onset of type 2 diabetes (Beck-Neilsen and EGIR, 1999). An understanding of research should lead to the development of strategies to target insulin resistance at a primary care level and thus reduce the number of people with type 2 diabetes and the associated complications.

FACT 1: A knowledge of insulin resistance is key to the understanding of type 2 diabetes

Insulin resistance plays a fundamental role in the pathogenesis of type 2 diabetes and its complications. Understanding insulin resistance enables us to effectively target ways of preventing both the development of type 2 diabetes and its major complications.

In essence, insulin resistance is a decrease in the sensitivity of tissues such as the liver, skeletal muscle and adipose tissue to the action of insulin. In the liver the result of impaired sensitivity to insulin is an increase in hepatic glucose production. In the other tissues the result of insulin resistance is a decreased uptake of glucose. Both processes lead to a net rise in the blood glucose. The body's response to this rise in glucose levels is for the ß cells to secrete more insulin. The first progression towards type 2 diabetes therefore is a hyperinsulinaemia and impaired glucose tolerance (IGT), with increases in post prandial glucose concentrations. Most patients stay at this level for a considerable time with the excess insulin produced just matching the blood glucose levels.

However, in time the ß cells begin to fail and are unable to produce sufficient insulin to stabilise the raised blood glucose, leading to the development of type 2 diabetes. Insulin resistance affects about a quarter of the population and one in seven adults have IGT (Reaven, 1994); 50% of these patients develop diabetes within 10 years.

FACT 2: Insulin resistance is the major risk factor for cardiovascular disease in type 2 diabetes

Cardiovascular disease causes 70–75% of deaths in people with type 2 diabetes (Kings Fund Policy Institute, 1996). Insulin resistance increases the risk of cardiovascular disease, preceding the actual development of type 2 diabetes. Patients with hyperinsulinaemia have been shown to have an increased risk of cardiovascular disease (Ruige et al, 1998). The reason for this increased risk lies with the metabolic and systemic changes associated with insulin resistance: insulin resistance syndrome.

The key features of insulin resistance syndrome are:

- Hyperinsulinaemia and impaired glucose tolerance (IGT). Increased cardiovascular

ARTICLE POINTS

1 Insulin resistance is the main risk factor for cardiovascular disease in people with type 2 diabetes.

2 The insulin resistance syndrome comprises hyperinsulinaemia and impaired glucose tolerance, hypertension, dyslipidaemia, central obesity, an increase in the severity of atherosclerosis and increase in blood coagulability.

3 Lack of exercise and obesity are the most important environmental risk factors for insulin resistance.

4 Understanding insulin resistance leads to rational use of drug treatment in people with type 2 diabetes.

KEY WORDS

- **Insulin resistance**
- **Cardiovascular disease**
- **Environmental factors**
- **Oral hypoglycaemic agents**
- **Coagulation defects**

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1 A combination of raised triglycerides, a low HDL cholesterol and an increase in small dense LDL cholesterol results in an atherogenic mix which substantially increases the risk of cardiovascular disease.

2 Evidence shows that insulin resistance may act directly via pathways in vascular smooth muscle cells to promote atherosclerosis.

3 Insulin resistance can be reduced within a few days of introducing a low calorie diet, even before much weight loss has occurred

4 Smoking is associated with hyperinsulinaemia and an increase in insulin resistance.

5 There is an argument for using metformin from diagnosis, as this targets the whole risk of cardiovascular disease rather than just hyperglycaemia.

risk has also been demonstrated in patients with IGT (Jarrett et al, 1982).

- Hypertension. This is a well known cardiovascular risk factor, particularly important in people with diabetes. Insulin can produce vasodilation in normal patients and this vasodilation is impaired in people with insulin resistance. Hyperinsulinaemia can result in increased reabsorption of sodium and water by kidney tubular cells and an overactive sympathetic system has also been postulated as one of the causes of hypertension in the obese insulin resistant patient (Ginsberg, 2000).
- Dyslipidaemia may be the most serious effect of insulin resistance. Insulin results in free fatty acids being released from adipose tissue into the bloodstream. The liver responds by increasing triglycerides, and this increases high density lipoprotein (HDL) excretion, lowering the HDL cholesterol. These changes also result in a shift of low density lipoproteins (LDL) to a more atherogenic form: small dense LDL. The net result is a combination of raised triglycerides, a low HDL cholesterol and an increase in small dense LDL cholesterol: an atherogenic mix known to substantially increase the risk of cardiovascular disease.
- Obesity (more correctly central obesity) is another component of insulin resistance syndrome. Obesity is a risk factor for cardiovascular disease and for the development of type 2 diabetes.
- Acceleration and increase in severity of atherosclerosis. There is evidence that insulin resistance may act directly via pathways in vascular smooth muscle cells, to promote atherosclerosis (Ginsberg, 2000)
- Increase in blood coagulability, with impaired fibrinolysis (see *fact 8* for more information).
- Hyperuricaemia is included by some as part of the syndrome.

FACT 3: The two most important environmental factors for insulin resistance (and type 2 diabetes) are lack of exercise and obesity

The increasing prevalence of type 2 diabetes is in no small part due to the increased insulin resistance in our population, as we become increasingly obese and take less exercise. Insulin resistance can be reduced within a few days of introducing a low calorie diet, even before much weight loss has occurred (American Diabetes Association, 1998). Subsequent weight loss further improves insulin sensitivity. Exercise, particularly vigorous exercise, reduces insulin resistance, although this effect is lost quickly (within 5 days) if exercise ceases (American Diabetes Association, 1998).

FACT 4: Smoking increases the risk of insulin resistance

Smoking is associated with hyperinsulinaemia and an increase in insulin resistance (Facchini et al, 1992). Smokers are also known to have a greater degree of abdominal fat (i.e. increased waist to hip ratio) than non-smokers (Shimokata et al, 1989). Reducing smoking improves insulin resistance, including the above associations such as dyslipidaemia.

FACT 5: Insulin resistance influences your choice of oral hypoglycaemic treatment

The sooner we target insulin resistance, the sooner we target cardiovascular risk. This means starting with metformin, which targets insulin resistance, rather than a sulphonylurea. It should also mean starting metformin as early as possible and not waiting for more than 3 months diet treatment before intervening pharmacologically. There is an increasing argument for using metformin from diagnosis as this targets the whole cardiovascular risk rather than just hyperglycaemia. We have scientific validation for the cardiovascular protective effect of metformin from UKPDS. Patients treated with metformin had a lower risk of myocardial infarction compared to patients treated with intensive therapy with sulphonylureas or insulin (UKPDS, 1998).

A similar argument applies to add-on therapy. If metformin does not lower HbA_{1C} sufficiently, the next oral hypoglycaemic agent to consider may be the glita-

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1 Insulin resistance precedes type 2 diabetes by many years so it is not surprising that 50% of patients with type 2 diabetes have complications at diagnosis.

2 There is now a strong case for all people with diabetes being prescribed a statin regardless of their cholesterol concentration.

3 The management of dyslipidaemia can be made easier by choosing oral hypoglycaemic agents that target insulin resistance.

4 Evidence shows that cardioprotective and renoprotective actions of ACE inhibitors and sartans are independent of blood pressure reduction.

5 The altered coagulation profile in people with type 2 diabetes has been underestimated as a cardiovascular risk factor and needs further research.

zones, another group that acts by reducing insulin resistance.

Given that insulin resistance precedes type 2 diabetes by many years it is not surprising that 50% of patients with type 2 diabetes have complications at diagnosis (UKPDS, 1990). We are moving towards treating before frank diabetes develops and could yet see a place for metformin earlier in the pathway leading to diabetes.

FACT 6: Targeting dyslipidaemia effectively means a rational choice of oral hypoglycaemic agents as well as specific drugs for dyslipidaemia

The Heart Protection Study showed how successful statins can be at reducing the risk of cardiovascular events in people with diabetes (Heart Protection Study Collaborative Group, 2002). There is now a strong case for all people with diabetes being prescribed a statin regardless of their cholesterol concentration. Certainly, you should aim for a total cholesterol <5 mmol/l with an LDL cholesterol <3mmol/l.

As already noted, it is equally important to address the raised triglycerides/low HDL cholesterol combination and statins are ineffective at addressing this risk. A fibrate could help here but the combination of fibrate and statin has possible serious side effects (myositis).

The management of dyslipidaemia can be made easier by choosing oral hypoglycaemic agents that target insulin resistance. Metformin has beneficial effects on lipids and so do the glitazones, particularly pioglitazone. In one study using pioglitazone in people with type 2 diabetes, pioglitazone produced a 22.5% reduction in triglycerides, an increase in HDL cholesterol of 6%, a decrease in total cholesterol of 4% and a decrease of LDL cholesterol of 4% (Boyle et al, 2002). Rosiglitazone may raise HDL cholesterol but it can also raise LDL cholesterol (NICE, 2000).

FACT 7: Insulin resistance may affect the choice of treatments for hypertension in people with type 2 diabetes

As well as affecting the choice of drugs for hyperglycaemia and dyslipidaemia, insulin resistance may affect the choice of antihypertensive treatment. Drugs such as ß blockers and thiazides can exacerbate insulin resistance whereas ACE inhibitors and alpha blockers may reduce insulin resistance (Krentz, 1996). The HOPE investigators observed that treatment with an ACE inhibitor is associated with a reduced onset of new onset diabetes (Yusuf, 2000). There is increasing evidence that cardioprotective and renoprotective actions of ACE inhibitors and sartans are independent of blood pressure reduction.

There are many postulated mechanisms for these protective effects, including effects on the endothelium and arterial wall, some of which may be mediated through mechanisms arising as a result of insulin resistance and its metabolic changes. The relationship between these drugs and insulin resistance has yet to fully unfold.

FACT 8: Coagulation defects in insulin resistance are another factor increasing cardiovascular risk

The altered coagulation profile in people with type 2 diabetes has been underestimated as a cardiovascular risk factor and needs further research. Insulin resistance is associated with increased fibrinogen levels, plasminogen activator inhibitor-1, tissue-type plasminogen activator antigen, factor VII and factor XII. Fibrinogen is a strong predictor of myocardial infarction and stroke in people without diabetes and increased levels are associated with vascular complications in people with diabetes (Ganda and Arkin, 1992). The best current strategy to combat these changes is to target insulin resistance.

With its well established record in preventing cardiovascular disease, aspirin is recommended by NICE in people diagnosed with type 2 diabetes. As a secondary preventive treatment it can be used for people with cardiovascular disease who should take 75mg daily. In terms of primary prevention, people with a 10 year coronary risk of greater than 15% should take 75mg aspirin daily (NICE, 2002).

FACT 9: There is no easily available test for insulin resistance in primary care, so we must identify insulin

resistance risk factors early

Insulin resistance can be measured by invasive techniques (involving catheters and infusions), or more practically by using fasting glucose and insulin measurements. However, as measuring plasma insulin levels is yet to become daily practice in primary care, we must focus on identifying risk factors early. In particular, in patients with IGT we must aggressively target factors such as dyslipidaemia and hypertension.

FACT 10: Managing insulin resistance is easier by means of a checklist to ensure you are continually targeting the main risk factors

Whenever considering insulin resistance, remember the simple checklist BAGODES:

- Blood pressure
- Aspirin
- Glycaemia
- Obesity
- Dyslipidaemia
- Exercise
- Smoking

A simple checklist like this will ensure that healthcare professionals do not miss out on important interventions with individual patients.

Conclusion

We now understand that insulin resistance poses a major risk in type 2 diabetes. By effectively targeting insulin resistance much can be achieved in primary care to reduce the excess risk of diabetes in our patients. These ten key facts should serve as the starting point for developing a strategy to target insulin resistance within practices and primary care organisations. ■

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PAGE POINTS

1 Measuring plasma insulin levels is yet to become daily practice in primary care so we must focus on identifying risk factors of insulin resistance.

2 A simple checklist could ensure that healthcare professionals do not miss out on important interventions with individual patients.

3 Through effective targeting of insulin resistance, much can be achieved in primary care to reduce the risk of type 2 diabetes.