INSULIN RESISTANCE: The Link Between Diabetes and Cardiovascular Disease

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As everyone with diabetes knows, insulin is the most important hormone controlling the blood glucose level, with effects particularly directed to muscle, fat and liver; it facilitates the flow of glucose from the blood stream into muscle or fat – and it reduces the flow of glucose out of the liver into the blood.

The effect of insulin on these critical tissues is mediated by the insulin molecule in the blood stream binding to a 'receptor' on a muscle, fat or liver cell; the receptor then activates several biochemical pathways controlling glucose entry to the cell as well as glucose storage and metabolism.

It has been known for several decades that a poor response of the body's tissues to insulin – called 'insulin resistance' – is of major importance in the development of type 2 (mature onset) diabetes.

More recently, it has become apparent that insulin resistance, even without diabetes, is associated with abnormal cholesterol levels, higher blood pressure and increased risk of cardiovascular disease.

Many people develop insulin resistance. In some, insulin production by the beta cells of the pancreas declines, leading to the development of diabetes. In others, apparently with 'healthier' beta cells, increased insulin production compensates for the insulin resistance and diabetes does not develop. Nevertheless, these people have a significant metabolic disturbance and increased risk of cardiovascular disease.

Interestingly, women with the polycystic ovary syndrome, who are usually overweight and have irregular menstrual periods and a degree of infertility, have insulin resistance which is an exacerbating factor in the dysfunction of their ovaries. Treatment of their insulin resistance can often improve their menstrual cycle and fertility.

What Causes Insulin Resistance?

A number of rare disorders such as genetic abnormalities of the insulin receptor or antibodies against the insulin receptor can cause insulin resistance, which is often very severe.

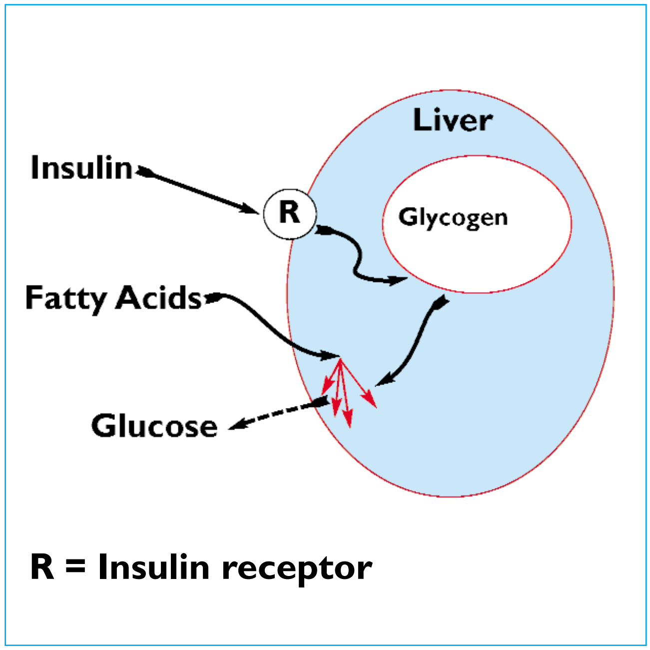
In the vast majority of people, however, the exact cause has not been found, but we know quite a lot and are rapidly learning more. Firstly, we know that the insulin receptor itself is not usually at fault – but rather a block in the signalling pathways in the cell which are activated by the receptor.

We also know there is a close relationship between fat metabolism and insulin resistance. In particular, insulin resistance is closely associated with accumulation of fat in the abdomen (visceral fat).

Abdominal fat cells are different from fat elsewhere in the body; they more readily accumulate fat (fatty acids) from the blood stream after a meal, and more readily release fatty acids into the blood stream at other times. As blood flows directly from intra-abdominal tissues to the liver, and as fatty acids increase glucose production from the liver, it is easy to understand how intra-abdominal fat could oppose the action of insulin on the liver and increase glucose production (see figure 1).

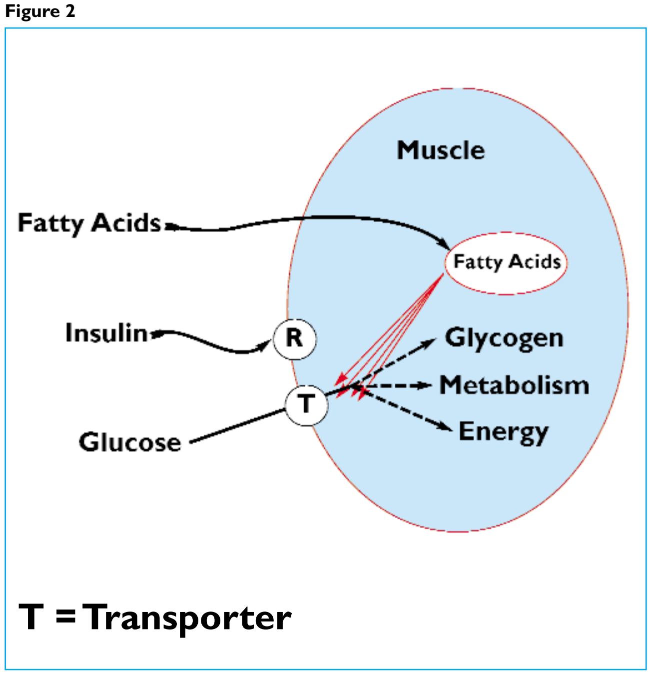
Also, accumulation of fat in muscle cells is associated with reduced insulin signalling; so it seems likely that excess fatty acids flowing from intra-abdominal fat contribute to the accumulation of fat in muscle and the blocking of insulin action (see figure 2).

Figure 1



Insulin normally controls the output of glucose by the liver. Fatty acids inhibit this action.

Figure 2



Insulin normally activates transporters to allow glucose to travel from the blood stream into the muscle cell. It also activates the pathways of glucose storage in the form of glycogen. Insulin also activates glucose metabolism to produce energy. Fatty acids,either in the muscle or coming from the blood stream, inhibit all these effects of insulin.

However, fat may contribute to insulin resistance in another way. Fat cells produce hormones which are released into the bloodstream. At least two such hormones (tumour necrosis factor α and the newly identified resistin) have the capability of blocking the effect of insulin in other tissues. The more fat cells there are, and the more they are loaded with fat, the more these hormones are produced.

The close connection between fat metabolism and insulin resistance may explain why insulin resistance is associated with adverse changes in blood lipids (fats) – especially high triglycerides and low HDL cholesterol (‘good’ cholesterol).

Once diabetes has developed, the high blood glucose level itself can also contribute to insulin resistance (this can happen in type 1 as well as type 2 diabetes). High glucose levels increase the production of a molecule called glucosamine in various tissues. Glucosamine seems to be important in blocking effects of insulin on glucose metabolism.

Why are some People Insulin Resistant?

As indicated above, the battle against insulin resistance is very much a battle against fat accumulation, especially abdominal fat. We know the following things are important:

Genes: There is a genetic, or hereditary, contribution to insulin resistance which may be partly due to a genetic determination of body fatness in addition to an equally strong genetic determination of fat distribution in the body. So, some people are genetically prone to accumulate abdominal fat, which is important in generating insulin resistance.

Gender: Although women generally have 30 to 40 percent more fat on their body than men, women who have not reached menopause have about half as much intra-abdominal fat as men – and have a much better response to insulin. Unfortunately, after menopause, women lose this advantage which suggests that the pre-menopause benefit is related to oestrogen.

Diet: Excess food intake, whether it be carbohydrate, protein or fat, leads to fat accumulation and insulin resistance. There is some evidence that the quantity and type (saturated fat) of fat in the diet also contribute to insulin resistance, but human research studies suggest that the total calorie or energy intake is more important than the fat content. Of course, it is easier to maintain a lower calorie intake and avoid obesity if the diet is low in fat.

Exercise: Regular physical activity is extremely important in preventing insulin resistance and works in several ways. Firstly, it causes muscle to produce more glucose transport proteins which are stimulated by insulin to help the flow of glucose from the blood into muscle cells. Secondly, exercise increases blood flow through muscle and the biochemical machinery (enzymes) which convert glucose into energy. However, perhaps the most important effect of exercise is to reduce accumulation of intra-abdominal fat.

Medications: There are a small number of medications (eg, cortisone) which antagonise the effect of insulin and contribute to insulin resistance.

What Can be Done to Prevent or Treat Insulin Resistance?

At present, we are unable to change our genes and most of us would not wish to change sex. However, we can exercise more and eat less. In fact, if communities who have a relatively inactive lifestyle with plenty of food could be persuaded to exercise more and eat less there would be a dramatic reduction in the catastrophic 'epidemic' of type 2 diabetes.

The Benefits of Oral Agents

Once diabetes has developed, two medications can substantially improve insulin action. One of these, metformin, has been available for about 50 years and is extremely useful in treating type 2 diabetes. Although metformin has been used for a long time, it is still not clear exactly how metformin improves insulin action, but it does not cause weight gain (which is a problem with most diabetes medications).

Recently, a new class of drugs has become available which profoundly improve insulin action in people who are insulin resistant; these are the thiazolidinediones or 'glitazones'. The glitazones have important effects on fat cells and fat metabolism which may be the main mode of action – but research is still unravelling the complexity of their effects. They work in a different way to metformin so metformin and the glitazones can be used together and help each other in improving insulin action.

Short term studies with the glitazones have shown that not only is insulin action improved but other phenomena which are related to cardiovascular disease are improved as well. So there is great interest in whether these drugs will not only help control type 2 diabetes, but also decrease the risk of cardiovascular disease. Longer term studies are needed to determine whether this hope will be fulfilled.

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