The National Severe Insulin Resistance Service

Severe Insulin Resistance

What is severe insulin resistance?

Insulin is a hormone (a chemical signal that travels in the bloodstream) made by the pancreas. It controls how the body uses sugars and fats and is essential for life. Its absence is the underlying problem in Type 1 diabetes. However, from person to person there are significant differences in how sensitive the tissues of the body are to insulin. In other words, in some people a very small amount of insulin produces a large change in the blood levels of glucose and fats (these people are said to be very insulin sensitive), while in others much larger amounts are required to produce the same change (these people are said to be insulin resistant). Those with severe insulin resistance are those whose bodies respond least well to insulin. Although many with severe insulin resistance do go on to develop diabetes, severe insulin resistance is NOT the same as diabetes: as long as the pancreas can produce enough insulin to overcome the insulin resistance, diabetes does not develop. However even before diabetes appears, insulin levels in the body may be extremely high, and this can produce a range of different problems in its own right.

What are the causes of Severe Insulin Resistance?

Rarely, people are born with severe insulin resistance and remain severely insulin resistant throughout their lives. Far more frequently insulin resistance develops only at puberty or in later life, while in some people it is only a temporary condition caused by other situations or illnesses. Most commonly a tendency towards insulin resistance is inherited, but only in the presence of environmental or lifestyle factors does it become a problem.

There are many different types and causes of severe insulin resistance. One way to group these is by the extent to which they are inherited or acquired, and the extent to which they reflect problems with fat (adipose) tissue.

The importance of inheritance in Severe Insulin Resistance

Various pieces of evidence demonstrate that inheritance is a very strong influence on the development of severe insulin resistance. Several different genes have been shown to carry abnormalities producing severe insulin resistance so far, and many others remain to be discovered. The strength of the effect of abnormalities in these genes is very variable.
Insulin Receptor defects

The most severe insulin resistance results from genetic alterations in the gene for the insulin receptor. Where these alterations almost completely destroy the function of the receptor, a condition called Donohue Syndrome results. In Donohue syndrome, affected babies are usually small, and have metabolic problems including failure to gain weight, and both low and high blood glucose, from birth. Sadly the severity of the insulin resistance in these babies means that some do not survive beyond the first year of life. When the insulin receptor is not quite so badly affected, insulin resistance may only be noted in childhood, often because of problems such as poor growth, excessive hair production, and early appearance of poor quality teeth. This condition is often known as Rabson Mendenhall Syndrome and affected patients often develop diabetes in the first or second decades of life. This diabetes is often very difficult to control, and can give rise to early complications. In almost all cases Donohue Syndrome and Rabson Mendenhall Syndrome result from inheritance of genetic alterations from both parents, and are more likely if the parents are blood relatives.

More commonly inherited changes in the insulin receptor gene only become apparent after puberty, often due to excess hair growth and irregular periods in women, who also sometimes are aware of darkening and thickening of the skin in the neck and other body creases. This condition is sometimes known as Type A insulin resistance. Although diabetes does usually develop and requires large amounts of insulin, strict control of diet and weight and regular aerobic exercise can have a major effect on diabetic control and the other effects of insulin resistance in this situation. Sometimes this also involves inheritance of genetic alterations from both parents, but often only one altered gene is required, and in this case there is often a history of diabetes in the family.

Lipodystrophy

The other major known genetic causes of severe insulin resistance are associated with abnormal fat distribution, and are discussed in the “Lipodystrophy” information leaflet in more detail. In these conditions the diet and lifestyle appears to be particularly important, and there is more variability between the severity of insulin resistance between affected patients. However it is likely that there remain many undiscovered inherited causes of severe insulin resistance, and it is a major goal of our research to uncover these.

The importance of lifestyle and the environment in Severe Insulin Resistance

Although inheritance plays a highly important role in insulin resistance, it is also clear that for the vast majority of people, insulin resistance becomes severe only when a genetic tendency interacts with other factors. These factors may be unavoidable and natural, including puberty and pregnancy, which both produce insulin resistance that may become extreme in some people, but many others relate to lifestyle.
By far the greatest influence on insulin sensitivity is excess accumulation, discussed below. However lack of exercise itself, even without changes in bodyweight, and the composition of the diet (e.g. high fat diets) can also further impact the body’s response to insulin. Other factors that influence insulin sensitivity, and that can interact with inherited factors, include severe infections or other medical stresses, and use of medications such as steroids for anti-inflammatory effect. The importance of all these environmental influences on insulin sensitivity is that even in those with inherited forms of severe insulin resistance, it is usually possible to significantly reduce the consequences of the condition (such as development of diabetes) with a healthy diet and plenty of aerobic exercise.

The Importance of fat (adipose) tissue in Severe Insulin Resistance

The amount of fat (adipose) tissue, and whether it is functioning normally, is critical for insulin sensitivity. Either too much fat (obesity) or an abnormal lack of fat (lipodystrophy) may lead to insulin resistance. Lipodystrophy is discussed in more detail in the “Lipodystrophy” information leaflet.

Excessive fat – that is, overweight or obesity – is by far the commonest cause of severe insulin resistance, and many patients who are obese and severely insulin resistant go on to develop diabetes. While most people become more insulin resistant as they gain weight, there is a large variation in the severity of this: some can become very obese and yet remain fairly insulin sensitive, while others are very sensitive to weight gain, and rapidly become very insulin resistant with only modest weight gain. This variable tendency to suffer metabolic problems with gain in weight is likely to be determined by inherited factors. While family history of overweight and diabetes may give a clue to an individual’s tendency to become insulin resistant with weight gain, the only safe option is to try to maintain a lean body weight. The insulin resistance of overweight/obesity appears to be largely reversible, and weight loss in susceptible individuals can have major benefits in terms of insulin sensitivity.

From a research point of view, we are very interested in understanding the interaction between genes and environment which commonly leads to people becoming insulin resistant with weight gain. However because many different genes are likely to be involved, most of our genetic studies focus on the much rarer people who are extremely insulin resistant but still slim, as we know from experience that single genes, which are easier to find, are more likely to be defective in that situation. We hope that lessons gained from studying rare types of insulin resistance will increase our understanding of commoner insulin resistance with obesity also.
What problems do people with Severe Insulin Resistance have?

Metabolic Problems

Hypoglycaemia
Although most doctors are aware of insulin resistance as a feature of diabetes (which means high blood glucose levels), many people with severe insulin resistance experience significant problems with hypoglycaemia, or low blood glucose, particularly before diabetes develops, and often this can be unrecognised or attributed to faints or even epilepsy. Most commonly hypoglycaemia may occur around two hours or more after eating. Early symptoms as blood glucose falls include sweatiness, a feeling of hunger, palpitation, or light-headedness. When it becomes more severe it may lead to drowsiness or blackouts. A characteristic feature is that these symptoms resolve quickly after eating sugary food or having a sweet drink. A prolonged oral glucose tolerance test (OGTT) with measurement of insulin will provide a strong clue to this diagnosis and will also permit diagnosis of severe insulin resistance.

Diabetes
As long as the pancreas is able to make enough insulin to overcome the body’s insulin resistance, diabetes does not develop. In fact, even in some patients with severe insulin resistance it may take decades before diabetes appears. However severe insulin resistance does usually lead to diabetes eventually when the pancreas gets “tired” and is unable to continue to produce adequate insulin. Times at which this is particularly likely to happen are at puberty and during pregnancy. In practice, anyone who has been identified as having severe insulin resistance should be monitored regularly (e.g. annually or in the event of any symptoms appearing) for the development of diabetes, and particularly closely during such high risk periods. Once diabetes develops it may eventually require large amounts of insulin to keep under good control.

Cholesterol and Triglycerides
Insulin action is vital not only to the metabolism of glucose, but also to the way the body handles cholesterol and triglycerides, another important class of fat. In general people with severe insulin resistance are no more likely to have elevated levels of “bad” cholesterol (LDL cholesterol) than anyone else, however low levels of protective “good” cholesterol (HDL cholesterol) are the norm, often combined with elevation of triglyceride. These abnormalities should be assessed in the light of overall long-term risk of heart disease or stroke, and treated where the risk is unacceptably high. Patients with lipodystrophy as well as severe insulin resistance often have much more severe elevation of triglycerides, which is discussed in more details in the lipodystrophy information sheet.
Liver problems
Excessive storage of fat in the liver is a common feature of many types of severe insulin resistance, and can lead to inflammation in the liver (hepatitis) and sometimes even to irreversible liver scarring (cirrhosis). This tends to be particularly severe in patients who also have lipodystrophy.

Cardiovascular problems
Because patients with severe insulin resistance often have diabetes, a low level of the healthy type of cholesterol (HDL cholesterol) and high levels of triglyceride in their bloodstream, their risks of heart attacks and strokes are significantly increased. Much of the treatment given aims to minimise the long term risk of these problems, although at the time of treatment symptoms are often not apparent.

Sex hormones and fertility
High insulin levels in the blood result when the pancreas tries to overcome insulin resistance by making more insulin. High insulin levels change the balance of male and female hormones produced by the ovary. The main problems which result are irregular periods, sometimes associated with extra hair growth in a male-type distribution, and development or worsening of acne. The actions of high levels of insulin on the ovaries sometimes impair ovulation, which can lead to problems with fertility. This combination of problems is very similar to that seen in polycystic ovary syndrome, which to some degree may affect up to 5% of women of reproductive age. There is no evidence that severe insulin resistance affects sex hormones or fertility in men.

Appearance
In some people who have severe insulin resistance in association with loss of fat tissue (lipodystrophy), loss of some of the normal contours of the face and body may lead to altered appearance. Please see the information sheet dealing with lipodystrophy for further discussion of this.

Almost all with severe insulin resistance develop a velvety thickening and darkening of the skin in natural skin creases called acanthosis nigricans, often also associated with multiple skin tags. This is usually particularly marked in the neck, under the arms and in the groin, although it can sometimes be more widespread. It is not a serious condition in its own right but can lead to further distress about the abnormal appearance.

Severe insulin resistance is often also associated with abnormalities in growth. In some cases, poor growth in childhood and reduced adult height are seen, while in others, accelerated growth can occur, sometimes with the early development of puberty. Sometimes severe insulin resistance leads to excessive growth of the body’s soft tissues, leading to a large tongue, hands and feet, coarse facial features and dental problems among other abnormalities (known as pseudoacromegaly). Because this combination is most commonly seen in adults producing too much...
growth hormone, patients with pseudoacromegaly have often been investigated for growth hormone overproduction before severe insulin resistance is recognised. The reason why some people with severe insulin resistance grow poorly, while others have problems with excessive growth are not understood, and this is an area of active research. The differences are most likely to result from the function of the particular genes which are abnormal in the different conditions.

**Treatments for Severe Insulin Resistance**

**Metabolic Problems**

**Hypoglycaemia**
Avoidance of foods which release large amounts of glucose into the bloodstream, such as white bread, pizza bases and other very processed carbohydrates, may markedly improve symptoms (details of ‘low glycaemic index diets’ may be found in a separate information sheet). Where this is not effective acarbose, a drug which reduces the absorption of sugars from the bowel, and which is also sometimes used to treat diabetes, may improve the symptoms of delayed hypoglycaemia following food.

**Diabetes**
Because severe insulin resistance is a fairly rare condition, no trials have looked at treatment of diabetes in this particular setting, and gathering evidence about this is a major aim of the Cambridge Severe Insulin Resistance Service. However it may reasonably be regarded as an extreme variant of Type 2 diabetes, and similar overall treatments used. Maintaining a healthy diet and bodyweight, and engaging in as much aerobic exercise as possible are critical aspects of controlling severe insulin resistance: even where there is a clear inherited cause for the condition, there may be particular sensitivity to bodyweight change and lack of exercise. Drugs which improve insulin sensitivity (principally metformin but sometimes also pioglitazone) are the mainstay of early medical treatment in people with very insulin resistant diabetes. Indeed there is a strong argument that using these agents before diabetes develops may delay its onset, although the absence of direct evidence for this means that this approach should be discussed with a specialist before a decision is made.

**Insulin Therapy**
Many with severe insulin resistance will eventually require treatment with insulin, and because they are very resistant to insulin, high doses may be required. It is important that sufficient doses of insulin are used to control blood glucose, however high those doses are, to prevent long term complications of diabetes. These high doses may not easily be accommodated by the size of insulin pens and other delivery devices, and so modifications of the usual approach may be required. This may be simply to use multiple injections at the same time, or to use vials and syringes rather than pens.
Sometimes specifically concentrated forms of insulin may be used, which allows smaller injection volumes. However these have to be prescribed on an individual basis by a specialist, and particular care needs to be taken not to give an accidental overdose of the more concentrated drug. Some patients with severe insulin resistance and difficult glucose control do very well with insulin pump treatment, sometimes even using the more concentrated insulin. However, once again, there are no formal trials proving that this is effective in severe insulin resistance, which means that this use of pump therapy is not yet approved by regulatory authorities.

**Cholesterol and other lipids**
A healthy diet and plenty of aerobic exercise should be the first strategy to treat abnormal cholesterol and triglyceride levels. In patients with lipodystrophy this is particularly important, and limiting dietary fat as much as possible appears to be the most important aspect of dietary treatment. Treatment with adequate doses of insulin sensitizing drugs and insulin if necessary to keep blood glucose controlled is also critical to optimizing blood lipids, and use of specific agents such as statins, fibrates and omega3 fatty acids is often also recommended.

**Cardiovascular**
As patients with severe insulin resistance seem to be at a higher risk of strokes and heart attacks, high blood pressure should be treated early and the early use of statins and aspirin as preventive medications should be considered on a case-by-case basis.

**Liver**
Strict adherence to a low fat diet should help slow down the progression of liver problems. Other experimental therapies are currently under trial.

**Hair growth, acne**
If mild, these can be managed with cosmetic measures and topical anti-acne medication. However if severe they may require the use of anti-androgenic medication, which is best dealt with in a specialist endocrine/metabolic clinic.

**Infertility**
Patients with lipodystrophy who are having difficulty getting pregnant need to be evaluated with their partners for other causes of infertility, as these are common and need to be excluded. It is best if couples are assessed and managed by a specialist.

**Cosmetic aspects**
The dark thickened skin (acanthosis nigricans) can sometimes be helped by strict adherence to diet and by drugs that improve insulin resistance. Formal psychological support may be necessary for some individuals.

Changing Faces is a UK charity that supports and represents people who have disfigurements of the face or body from any cause, whether from birth or acquired.)
The charity provides a free skin camouflage service which is an option if you would like to cover up your acanthosis nigricans. We can refer you to this service or you can self-refer.

Changing Faces also have many self-help guides about living with an appearance altering condition, they also provide psychological support.

Please see link below for further information or ask a member of our team to provide you with further information:
https://www.changingfaces.org.uk/get-support

Psychological Support
Living with a chronic disease, especially one that affects appearance, can be very challenging. Specialist psychological support may be helpful for some people. If you feel you would benefit from some psychological support, please let a member of the clinical care team know.

For further information please contact:
- Severe Insulin Resistance Office: 01223 768455
- Dietitians’ office: 01223 216655
- Lipodystrophy UK Support Group www.lipodystrophy.co.uk
- Lipodystrophy UK Facebook Group https://www.facebook.com/groups/LipodystrophyUK/

We are now a smoke-free site: smoking will not be allowed anywhere on the hospital site. For advice and support in quitting, contact your GP or the free NHS stop smoking helpline on 0800 169 0 169.

Other formats:
If you would like this information in another language, large print or audio, please ask the department where you are being treated, to contact the patient information team: patient.information@addenbrookes.nhs.uk. Please note: We do not currently hold many leaflets in other languages; written translation requests are funded and agreed by the department who has authored the leaflet.

Document history
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