The National Severe Insulin Resistance Service

Lipodystrophy

What is lipodystrophy?
Lipodystrophy refers to a group of conditions where the amount and/or distribution of fat tissue is abnormal. There is usually a lack of fat tissue in all or part of the body, sometimes with extra fat accumulating elsewhere. This is different from “thinness” or “fatness” which both result from changes in the amount of fat stored in normal fat cells. In lipodystrophy, the fat cells themselves are abnormal or even absent. Lipodystrophy leads to a changed physical appearance and frequently to other complications.

Different types of lipodystrophy
There are many different types and causes of lipodystrophy. Lipodystrophy can be most simply divided into forms that are inherited (passed down through families) and forms that are acquired.

Inherited lipodystrophies
The inherited lipodystrophies that are currently known about are in two forms:
- **Total/generalised lipodystrophy**, where all or almost all fat is absent, usually from birth.
- **Partial lipodystrophy**, where the lack of fat tissue is partial and does not affect all areas of the body. It may not become apparent until after puberty.

Inherited forms of total lipodystrophy
This is the more severe form of inherited lipodystrophy and involves a lack of almost all body fat. This condition is sometimes called congenital generalized lipodystrophy (CGL), or Berardinelli-Seip syndrome. In most (but not all) instances, this condition is caused by genetic alterations in one of two different genes (called seipin and AGPAT2). The conditions are inherited in an autosomal recessive manner. This means that affected people will have inherited one altered copy of the gene from their mother and one from their father.

The chance of an affected person passing on this form of lipodystrophy to their children is very low, unless their partner is related to them (such as cousins).

The diagnosis of these types of lipodystrophy usually becomes apparent at birth or in the first few months of life, often because affected children look very muscular due to the absence of fat.
As well as the abnormal appearance of lipodystrophy, patients suffering these conditions are at the severe end of the spectrum of metabolic problems which are associated with lipodystrophy.

Please let us know if you would like an information sheet with more information about how recessive genes are passed down in families.

**Inherited forms of partial lipodystrophy**

There is a group of inherited conditions where fat tissue is lost from only part of the body. While still uncommon, these conditions are much less rare than total lipodystrophy and are usually inherited in an autosomal dominant fashion. This means that each child of an affected person has a 50% chance of having the condition. Because the extent of fat loss is less widespread, these conditions are often more subtle, and commonly become apparent around the age of puberty. Furthermore, because women normally have more fat tissue than men, these conditions are much more commonly diagnosed at this stage in women, although there is an equal likelihood of men and women carrying the abnormal gene.

Please let us know if you would like an information sheet with more information about how dominant genes are passed down in families.

Several different genetic causes of this type of lipodystrophy are now known. The most common, sometimes known as Dunnigan type lipodystrophy or Dunnigan-Köbberling syndrome is caused by changes in the protein lamin A/C.

In this condition fat loss affects the arms, legs and trunk although characteristically the face and neck and labia are spared. Because of this, extra fat is often seen in the face and neck and also the labia in women.

Once again, problems associated with this condition can be divided into those relating to the lipodystrophic, muscular appearance of arms and legs and those caused by the metabolic complications of having reduced fat tissue. The metabolic complications may be less severe than in complete lipodystrophy and can be rather variable between people with the same genetic alterations. Women tend to be more severely affected than men.

Different alterations in the Lamin A/C gene are known to be associated with a range of other conditions including muscle weakness, heart valve problems, nerve damage and some other rarer conditions. Usually, specific genetic changes either cause partial lipodystrophy or those other conditions, although we do continue to learn about overlaps between them.

In our laboratory over the last few years we have also identified alterations in four further genes, which lead to partial lipodystrophy. These genes are PPARγ, PLIN1, CIDEC and AKT2. In these conditions the loss of fat tissue is most striking over the arms, legs and buttocks, with fat on the trunk usually unaffected.

These forms of partial lipodystrophy are also associated with metabolic derangements and other problems such as high blood pressure.
Some people who have inherited partial lipodystrophy do not fit into any of these genetic groups. One of our major research interests is in studying the genes of such people to look for new causes of lipodystrophy, which may lead to increased understanding of the condition, and hopefully in the long term may point to improved treatments.

**Acquired lipodystrophies**

**Acquired partial lipodystrophy**

This form of lipodystrophy is not thought to be inherited because there are rarely, if ever, other family members affected. It often occurs in childhood or early adolescence, but can occur at any age, often after a viral infection and is frequently associated with the presence of an antibody in the circulation that accelerates the “complement pathway”. This is a pathway normally required for the protection of the body against infection, but when abnormally activated may instead be damaging to the body itself. There is a progressive change in appearance with loss of fat from the face, upper limbs and upper trunk. Usually, however, the lower limbs and lower part of the trunk are spared. As these people often have quite a large amount of remaining fat, they often avoid the metabolic complications of lipodystrophy. This condition sometimes has associated kidney damage.

**Acquired total lipodystrophy**

Occasionally acquired partial lipodystrophy can progress to involve loss of all body fat. These people develop all the metabolic problems seen in congenital total lipodystrophy.

**HIV-associated lipodystrophy**

HIV infection and its treatment is the commonest cause of lipodystrophy worldwide. However, we do not see many patients with HIV-associated lipodystrophy in our clinic as the metabolic problems associated with it tend to be relatively mild, so it shall not be discussed further here.

**What problems do people with lipodystrophy have?**

**Appearance**

The normal contours of the face and body are partly determined by fat tissue. When fat tissue is absent, reduced or abnormal in shape then alterations in appearance occur. These may be distressing, particularly in females who normally have a greater amount of fat under the skin. For reasons that are not well understood, people with lipodystrophy quite often have enlargement of muscles, especially in legs and arms, leading to an athletic appearance.

In women the lack of fat can result in the absence of breast tissue and lack of fat on the hips and bottom. In some forms of lipodystrophy women may experience extra fat in their face and/or labia.

**Hirsutism/hair loss**

Some women with lipodystrophy have excess hair growth on their face and body (hirsutism), or may experience frontal scalp hair loss. This is due to raised male hormones caused by polycystic ovarian syndrome.
Acanthosis nigricans
Some individuals develop a velvety thickening and darkening of the skin in natural skin creases called **acanthosis nigricans**. 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.

**Metabolic problems**
Fat tissue is where we normally store any excess calories we consume and store this as a fatty substance called “triglyceride”. We depend on our triglyceride stores for our survival during periods of fasting. People who have more severe forms of lipodystrophy can develop a number of problems with their metabolism. They may find it difficult to fast for long periods, or to undertake prolonged exercise (although they may often be very good at shorter sprint-like activities). Any fat made by the body or eaten as part of the diet cannot be stored appropriately in fat tissue and therefore ends up in the wrong places, such as muscle, liver and pancreas. In these places it interferes with the normal action or production of insulin and **diabetes mellitus** often develops. This is often difficult to control as there may be severe insulin resistance. The triglyceride levels also build up in the blood (so-called **hypertriglyceridaemia**) and if these reach high levels they can appear on the skin as a rash (eruptive xanthoma) or, more seriously, damage the pancreas (**acute pancreatitis**).

**Liver problems**
In some cases, long standing excessive storage of fat in the liver can lead to inflammation in the liver (**hepatitis**) and sometimes to irreversible liver scarring (**cirrhosis**).

**Cardiovascular problems**
Because patients with lipodystrophy often have diabetes and high levels of fat in their blood stream they are more at risk of heart attacks and strokes. Much of the treatment given in lipodystrophy aims to reduce the long term chances of these problems as much as possible, 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, sometime 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 lipodystrophy affects sex hormones or fertility in men.

**Treatments for lipodystrophy**
There is currently no cure for any form of lipodystrophy, other than for some patients with HIV lipodystrophy in whom a change of antiviral drug regime can sometimes be beneficial.
However, patients with lipodystrophy can be helped in many ways to reduce the adverse impact of the condition on their health.

**Treatment of cosmetic aspects**
No drug treatment restores fat tissue where it is absent. In some cases, cosmetic surgery can be used to move fat tissue from one part of the body to another or artificial fillers can be used. The dark thickened skin (acanthosis nigricans) can sometimes be helped by strict adherence to diet and by drugs that improve insulin resistance (see below).

**Changing Faces**
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 acanthosis nigricans. We can refer you into 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](https://www.changingfaces.org.uk/get-support)

**Treatment of hypertriglyceridaemia**
A low fat diet is the mainstay of treatment of hypertriglyceridaemia. Failure to adhere to a low fat diet makes it very difficult if not impossible to control hypertriglyceridaemia. Physical activity is also important as increased activity can improve insulin sensitivity. Sometimes the use of drugs such as fibrates, statins or omega-3 fatty acids are advised.

**Treatment of diabetes**
Diet is an essential part of treatment for diabetes in patients with lipodystrophy. Limiting dietary fat and total calorie intake to within daily requirements is the most important aspect of dietary treatment. Failure to adhere to these dietary restrictions makes it very difficult to treat diabetes in people with lipodystrophy. Physical activity is also important.

Diet and physical activity alone may not be sufficient, and treatment with drugs such as metformin, pioglitazone, gliptins, SGLT-2 inhibitors, and GLP-1 agonists may be considered.

Many patients require insulin therapy, often in high doses because of insulin resistance.

**Metreleptin therapy**
Fat cells make leptin. Leptin is a hormone which is involved in appetite control. If leptin levels are low, as they are in many patients with lipodystrophy, appetite may be abnormally stimulated, leading to excessive food consumption, which can make metabolic problems worse.

Some patients with lipodystrophy may benefit from treatment with leptin therapy. Leptin therapy (Metreleptin or Myalept®) is most effective in people with total lipodystrophy where it improves diabetes control, hypertriglyceridaemia, and fatty liver. It has also been shown to be of some benefit in people with partial lipodystrophy and low leptin levels.
Metreleptin is injected under the skin once or twice daily.

Metreleptin is now licensed in Europe, but in the UK is currently only available on a named patient basis following individual patient approval by Amryt Pharma Plc.

**Treatment of cardiovascular problems**
As patients with lipodystrophy are at a higher risk of strokes and heart attacks, high blood pressure should be treated early and aggressively. The early use of statins and aspirin as preventive medications should also be considered on a case-by-case basis.

**Treatment of liver problems**
Strict adherence to a low fat, low calorie diet should help slow down the progression of liver problems. Fat build up in the liver is very common in people with lipodystrophy and can cause inflammation and scarring in the liver. Eventually this may progress to cirrhosis. In our opinion all people with lipodystrophy should have liver function tests and liver scans on a regular basis (at least annually). The latter should even be done in people with normal liver blood tests as these tests are not a sensitive marker of liver disease.

**Treatment of excess hair growth and 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 (medicines which block male hormones), which is best dealt with in a specialist endocrine/metabolic clinic.

**Treatment of infertility**
Patients with lipodystrophy who are having difficulty conceiving 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 in a specialist clinic.

**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 or you could contact your local IAPT (psychological therapies) service.

**Research**
If you are a new or follow-up patient with lipodystrophy we may ask you to consider entering our research studies. If you are interested in knowing any more about the studies please ask the doctor you see in clinic or contact us using the details at the end of this document.

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Website
http://www.cuh.org.uk/national-severe-insulin-resistance-service

Lipodystrophy UK Support Group  www.lipodystrophyuk.org

Lipodystrophy UK Facebook Group
https://www.facebook.com/groups/LipodystrophyUK/

Lipodystrophy United (US patient support group)  
https://lipodystrophyunited.org

Diabetes UK (UK Diabetes patient support group)  
https://www.diabetes.org.uk

Changing Faces  https://www.changingfaces.org.uk/

IAPT (Psychological Therapies) service.  https://www.nhs.uk/service-search/find-a-psychological-therapies-service/

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