Insulin resistance can be defined as an impaired responsiveness to the glucose-lowering response of insulin. It can be caused by several physiological and pathological conditions, the most common being obesity. Patients referred to the NSIRS have rare genetic or acquired conditions causing SIR and around 70% of the patients seen to date have lipodystrophy, a group of conditions that leads to the abnormal distribution of subcutaneous fat. Other patients have even rarer conditions, for example abnormal function of their insulin receptor, due to a genetic mutation, or antibodies against the insulin receptor. The NSIRS does not provide a service for patients whose primary cause of insulin resistance is obesity related, as they are better served by existing obesity services.

Specialist therapies, such as high-strength insulins, insulin pump therapy, metreleptin, GLP1-agonists or immunosuppression, may be offered if appropriate. We also offer surveillance and treatment of hyperlipidaemia, polycystic ovarian syndrome and appearance issues. Patients may require genetic counselling and we will often see several members of the same family together.
Our case studies

With the patients’ permission, the following cases give some real-life examples of these rare conditions and of the experiences of patients. Some names have been changed.

Case 1: Insatiable hunger – introducing metreleptin
Karen, (below), 54, (BMI 21.5kg/m²) with familial partial lipodystrophy Type 2 secondary to a mutation in the LMNA gene, was referred to the NSIRS with a 15-year history of poorly controlled diabetes (HbA1c 64mmol/mol) and hypertriglyceridaemia (7.3mmol/l). She was treated with oral antihyperglycaemia medication and a fibrate.

She was often hungry, but was making efforts to improve her diet by following a low-fat diet, as advised by the NSIRS dietitian. Her HbA1c came down from 64mmol/mol to 46mmol/mol with dietary changes. After starting on metreleptin therapy she reported an improvement in her hunger levels. Her blood glucose levels also normalised to HbA1c 42mmol/mol. Meanwhile, her triglyceride levels have now been reduced significantly to 1.6mmol/l.

What is lipodystrophy?
Lipodystrophy is a very rare condition with a number of genetic or acquired causes. It can affect the whole body (generalised) or part of the body (partial). Because women normally have more fat tissue than men, these conditions are commonly diagnosed in females during puberty, although there is an equal likelihood of men and women carrying the abnormal gene. There are currently only a limited number of identified genetic causes of lipodystrophy and genetic testing does not always provide a definitive diagnosis. So around 20% of the patients seen in the service, who have the clinical appearance of lipodystrophy, do not yet have a precise cause identified.

Lipodystrophy can affect both the physical and mental health of an individual. Physically, they may have:
• significant insulin resistance and difficult-to-control diabetes
• hypertriglyceridaemia and increased risk of pancreatitis
• polycystic ovary syndrome
• non-alcoholic fatty liver disease and cirrhosis
• cardiomyopathy.

The impact on mental health usually results from the difference in appearance arising from abnormal fat distribution.

What is leptin?
Leptin is a hormone produced by adipocytes which has a central role in energy homeostasis. Normally, a low leptin concentration signals starvation and increases hunger. As a result of the lack of adipose tissue, people with lipodystrophy may be deficient in leptin and therefore develop an insatiable hunger, due to a lack of satiety signals and hypertriglyceridaemia, ectopic liver fat accumulation and hyperglycaemia due to insulin resistance.

Leptin replacement injections (metreleptin, Myalept) may be offered to selected patients with lipodystrophy with a low leptin level and metabolic abnormalities. Metreleptin is used in combination with changes in diet and lifestyle, diabetes medication and lipid-lowering therapies. Patients have improvements in appetite reduction, triglyceride levels, with improved diabetes control with reduced insulin requirements.

I commenced leptin therapy about a year ago and this has made a huge difference to my life. My diabetes results and lipid profiles have improved immensely to the point where I do not have to worry about them anymore.”

Case study 2: Managing diabetes control or quality of life – or both?
Lynne (above), 51, (BMI 19.5kg/m²) was diagnosed with acquired generalised lipodystrophy, complicated by poorly controlled diabetes, hypertriglyceridaemia and recurrent pancreatitis. She was referred to the NSIRS in 2012. Following intensive review and education, and also after commencing metreleptin replacement therapy, she was requiring up to nine injections per week.
FEATURE

SEVERE INSULIN RESISTANCE

subcutaneous injections per day, and a total daily insulin dose of 152 units to maintain blood glucose levels in target. This caused severe discomfort at her injection sites, due to complete absence of subcutaneous adipose tissue. So after exceptional funding approval, insulin pump therapy was started, using a Medtronic 640G pump with 30° angle cannula sets.

Lynne’s pre-pump HbA1c was 43mmol/mol, but with frequent hypoglycaemia. Since starting pump therapy her HbA1c has remained within the target range. Her last result was 48mmol/mol, with significantly fewer episodes of hypoglycaemia, but the effect on her quality of life, due to reduced pain from injecting large frequent doses of insulin via a pen, has been the most valuable to her.

Insulin pump therapy in ‘non-Type 1’ diabetes

In the last three years we have been evaluating insulin pump therapy in selected patients with lipodystrophy and other causes of SIR. As these patients fall outside the NICE criteria for pump therapy, individual funding requests were required. As well as improved quality of life, another common theme noted in NSIRS pump users has been that their total daily insulin requirement is significantly lower compared with pre-pump.

There is also a marked drop in insulin requirements overnight, and increased bolus requirements with carbohydrate intake. To address this issue, we reduce the starting doses beyond the initial calculation and reduce the overnight basal from the start.

Improvements in HbA1c levels have been less convincing so far. This may be related to factors such as a lack of formal diabetes education, distance from the service or simply small numbers of patients (in our service) started on pumps. Within the service we now have seven patients using insulin pumps.

We plan to ensure that all patients who have approved funding for pump therapy in the NSIRS attend a carbohydrate awareness workshop. We also plan to measure the effect on quality of life of using anxiety and depression questionnaire scores pre and post pump therapy.

In time, with increased numbers, the benefits of insulin pump therapy in this group may become clearer.

Case study 3: Metabolic surgery

Barbara (below), 53, has familial partial lipodystrophy Type 1 with secondary diabetes and hepatic steatosis. Despite extensive input from the NSIRS team, she continued to struggle with her weight and diabetes management, so exceptional funding was requested for a Roux-en-Y gastric bypass (RYGB). The application was rejected, so she self-funded the procedure in 2016.

Her pre-operative BMI was 28kg/m², and her diabetes was suboptimally controlled with an HbA1c of 75mmol/mol on a total daily insulin dose of >150 units of insulin. Post surgery there was an improvement in her HbA1c to 54mmol/mol and she was able to stop insulin entirely and was taking metformin only. She will require 1g methyl prednisolone, rituximab and oral prednisolone. Four weeks after initiation of immunosuppressive therapy, Andrea had stopped insulin entirely and was taking metformin only. She will require 1g rituximab every six months for two years.

Since her treatment Andrea has gained weight (BMI 28.44kg/m²), and is feeling much better. Her last HbA1c was 32mmol/mol without any diabetes treatment. She has been advised to maintain blood glucose monitoring, around three to four times a week to observe for any deterioration. She may require further rituximab infusions if she shows any signs of relapse.

Reduction in energy intake in patients with lipodystrophy

One of the most important lipodystrophy treatments is the reduction of fat and carbohydrate in the diet and weight reduction. The SIRS specialist dietitians provide advice, based on each individual’s basal metabolic rate for their gender, age and weight. If unsuccessful, metabolic surgery may be suggested. Although the numbers of patients are small (five RYGB and one sleeve gastrectomy), we have had some very positive outcomes in patients with partial lipodystrophy’ which adds to existing positive case reports in the literature2–6.

Case study 4: How receptive is the insulin receptor?

Andrea, 30, (BMI 22.84kg/m²) was referred to our service with a six-month history of newly diagnosed diabetes with extremely high insulin requirements. She also had severe skin pigmentation (acanthosis nigricans), weight loss and severe clinical and biochemical hyperandrogenism. Three months after her diabetes diagnosis she was requiring hundreds of units of insulin a day, delivered at 22 to 25 units/hour via an insulin pump, with additional mealtimes bolus doses of 300 units Humalog U200 insulin via a KwikPen. She did not use the pump overnight due to overnight hypoglycaemia.

Andrea was found to have a high titre of anti-insulin receptor antibodies, confirming that she has Type B insulin resistance. This very rare condition is characterised by a rapid onset of severe hyperglycaemia, severe hyperinsulinaemia, acanthosis nigricans, weight loss and often severe hyperandrogenism in women. The lipid profile is usually normal and the adiponectin is high. Type B insulin resistance is often associated with the autoimmune condition systemic lupus erythematosus.

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54mmol/mol and was able to stop insulin treatment. However, the HbA1c has risen slightly to 60mmol/mol so she has increased her oral medication. Her BMI has reduced to 17.85kg/m². Her liver MRI shows that her liver fat has halved and hepatic stiffness has significantly reduced.

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Metabolic changes in patients with insulin receptoropathy compared with more common causes of insulin resistance

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Insulin receptoropathies

Other examples of insulin receptoropathy are those due to mutations in the insulin receptor for example those diagnosed in childhood with Donohue Syndrome and Rabson-Mendenhall Syndrome and less severely affected patients who are usually diagnosed in puberty/adulthood, also known as Type A resistance. Patients with insulin receptoropathies usually have a normal lipid profile and a high adiponectin, which is the opposite to the metabolic abnormalities in patients with lipodystrophies and/or the more common obesity-related insulin resistance syndromes.

People with lipodystrophy often report traumatic experiences, such as bullying at school or work, comments about their appearance from strangers... this can have a psychological impact, affecting self-esteem, relationships and self-management behaviour.

Not just the physical feelings

People with chronic conditions have an increased risk of developing mental health problems, with around 30% known to have a mental health condition. A rare disease increases this percentage to around 69%. A review of the clinical notes of NSIRS patients showed that 40% of patients with lipodystrophy are prescribed antidepressants compared with 10% to 20% in general Type 2 diabetes settings.

People with lipodystrophy often report traumatic experiences, such as bullying at school or work, abusive comments about their appearance from strangers or accusations of eating disorders or parental neglect due to their low BMI. All of this can have a significant psychological impact affecting self-esteem, relationships and self-management behaviour. In addition, being such a rare condition, there is limited awareness or understanding of lipodystrophy and other syndromes of severe insulin resistance among some healthcare professionals. This can result in a lack of trust, or feelings of frustration and anger, especially if affected patients are given conflicting advice.

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Improving Access to Psychological Therapies (IAPT) has enabled us to offer better support for mental health issues (see also article on page 18, this issue). The psychological wellbeing service is now available to NSIRS patients on a referral basis, but it does not meet the needs of everyone in our clinic, as they are not all local. We are continuing to collect data to support funding for psychology support specifically for the NSIRS.

Looking to the future

We are looking into addressing the need for support related to body image issues after patients highlighted this as an unmet need. We hope to pilot a support group later in the year to provide:

- strategies and mechanisms to deal with unwanted attention and comments
- relaxation techniques to reduce anxiety
- practical advice for clothing
- the opportunity to meet other people with lipodystrophy.

We have delivered a series of talks across England in Liverpool, Leicester, Durham, London (the Association of British Clinical Diabetologists), Warwick (HEART UK), and at the Cambridge Insulin Pump course in a bid to raise awareness of severe insulin resistance syndrome nationally. Presentations in the south-west are planned for 2019. Our website is being updated to include links to further information about lipodystrophy and other severe insulin resistance syndromes for both patients and healthcare professionals.

Over the coming year, we will also be evaluating proactive cardiac surveillance for lipodystrophy patients due to the increased risk of coronary artery disease.

Finally, after identifying a disproportionate geographical spread of patients we are now also offering telephone clinics for follow-up appointments in a bid to reduce the burden of long journeys.

Referral to the NSIRS

The NSIRS is provided for patients with lipodystrophy and/or severe insulin resistance. The service is funded by NHS England and there is no charge to referring clinical commissioning groups or hospital Trusts.

The referral criteria are as follows:

- Donohue Syndrome or Rabson Mendenhall Syndrome with confirmed severe hyperinsulinaemia
- clinically diagnosed lipodystrophy (generalised or partial)
- unexplained severe insulin resistance with: BMI<30kg/m² (BMI Z score <=+3 in children) and acanthosis nigricans and/or severe hyperinsulinaemia
REFERENCES


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