Severe insulin resistance: pathologies

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Abstract
In parallel with the increasing prevalence of obesity, rates of insulin resistance and its associated complications have increased; however, insulin resistance is not only a disease of the overweight and obese. Disorders of adipose tissue expandability and insulin receptor signalling cause syndromes of severe insulin resistance that may go unrecognised in clinical practice but whose metabolic complications are significant and often the initial presentation of the condition.

This review will discuss the differing pathologies mediating insulin resistance that may be seen in clinical practice and will outline the phenotypic characteristics that may allow their differentiation. Copyright © 2017 John Wiley & Sons.

Practical Diabetes 2017; 34(6): 189–194

Key words
severe insulin resistance; lipodystrophy; insulin receptor defects

Case 1
A 43-year-old woman had a diagnosis of type 1 diabetes. She was diagnosed with diabetes during pregnancy and remained dependent on insulin thereafter. Her past medical history also included coeliac disease, hypertension and hyperlipidaemia, specifically hypertriglyceridaemia. Her family history was significant for cardiovascular disease with both her sister and mother having had a myocardial infarction under the age of 50, respectively. She was noted by an allied health professional to have excess fat accumulated around her neck which differed greatly from her fat deposition elsewhere. The woman reported that she had always been thin with prominent musculature. Her medical therapy included multiple daily injections of insulin analogues (170 units/day), losartan and rosuvastatin.

On examination, her BMI was 23.7kg/m² and there was an absence of subcutaneous fat on her limbs and trunk, and reduced breast tissue. There was prominent fat around her neck and face and no other findings. Pertinent laboratory findings included HbA1c 54mmol/mol, triglycerides at 4.0mmol/L, HDL 0.98mmol/L, and LDL 1.89mmol/L; fasting insulin 107pmol/L (0–80), C-peptide 958pmol/L (174–960) in the setting of established diabetes mellitus. IA-2, islet cell and GAD antibodies were negative. Adipokines were measured: leptin 2.0ng/ml (BMI <25 [reference 2.4–24.4]) and adiponectin 1.7ug/ml (BMI <25 [reference 4.4–17.7]). Sequencing of the LMNA gene was undertaken and revealed a known heterozygous pathogenic mutation confirming a diagnosis of familial partial lipodystrophy type 2 (FPLD2) with secondary (not type 1) diabetes mellitus.

Case 2
Referral for assessment of a young girl at age 14 years who despite otherwise normal pubertal development had primary amenorrhoea that was complicated by hirsutism and deepening of her voice. On examination, the patient was lean with a BMI of 18.6kg/m² and had marked acanthosis nigricans with no evidence of subcutaneous fat loss. A pelvic ultrasound revealed polycystic ovaries. Her testosterone was elevated at 5.7nmol/L (0.0–1.8), LH 8.9U/L (1.3–8.4), FSH 4.9U/L (2.9–8.4). The patient was normoglycaemic with fasting glucose 4.1mmol/L and insulin 687pmol/L (0–80). Lipid profile was normal; triglycerides 0.8mmol/L (0.3–1.8) and HDL 2.75mmol/L. Leptin at 12.6 (BMI <25kg/m² [reference 2.4–24.4]) and adiponectin at 15.0 (BMI <25kg/m² [reference 4.4–17.7]) were both normal. Congenital adrenal hyperplasia was excluded.

This patient had clinical features of severe insulin resistance and elevated fasting insulin levels. Normal lipids and adiponectin levels were suggestive of a complete defect in insulin signalling. Sequencing of the insulin receptor gene (INSR) revealed a pathogenic heterozygote mutation in the insulin receptor.


**What is insulin resistance?**

Insulin resistance (IR) refers to a state where there is a reduced biological effect of a given insulin concentration. Early descriptions of what we now know as insulin resistance arose from observations of the responsiveness of subjects with diabetes mellitus to insulin administration. Himsworth reported on what he described as insulin-sensitive and insulin-insensitive diabetic patients based on the ability of exogenous insulin to mediate glucose disposal. Researchers capitalising on the development of the insulin radioimmunoassay quantified endogenous insulin levels among individuals with diabetes mellitus and identified a subset with disproportionately high circulating insulin levels for the degree of glycaemia. Those who were deemed insensitive to insulin were typically overweight and older; these observations with others subsequently formed the basis of the modern characterisation of diabetes into type 1 and type 2.

**What causes IR and why is IR clinically important?**

Insulin resistance is of major clinical importance as it has been implicated in the pathogenesis of a number of life-limiting conditions including diabetes mellitus, cardiovascular disease, non-alcoholic fatty liver disease (NAFLD) and cancer. Severe IR in an individual is usually explained by one of two pathological processes, the first due to impaired ability of adipose tissues to store excess energy as fat. This includes both obesity and lipodystrophy. Both can cause lipotoxicity induced by ectopic fat deposition in muscle, liver and pancreas which is implicated in causing IR. A second and much less common cause occurs due to impairment of insulin receptor signalling. Irrespective of the aetiology there is significant overlap in the clinical phenotype of these conditions. Awareness of IR is important in order to identify and manage those at highest risk of adverse events. While IR is prevalent in the general population particularly with current trends in obesity, it is also important for the clinician to be able to identify patients with possible syndromes of severe insulin resistance (SIR). The diagnosis and differentiation of SIR syndromes are important for implementing interventions to improve insulin sensitivity, treat the metabolic complications and identify heritable causes where genetic counselling may be necessary. Many patients with SIR syndromes present in general diabetes and endocrinology clinics. Piecing together a number of clinical and biochemical clues usually suggests the diagnosis before confirmation with genetic or immunological testing. The above Cases 1 and 2 demonstrate how the use of a multifaceted approach to assessing individuals with suspected IR can allow differentiation of SIR syndrome subtypes. Insulin resistance phenotypes have also been described in a number of syndromic disorders, e.g. premature aging syndromes; their discussion is beyond the scope of this review.

**Clinical features of IR**

**Impaired glucose regulation**

Impaired glucose tolerance and overt diabetes mellitus commonly occur in states of IR. The physiological response to overcome the effect of IR is an increase in pancreatic beta-cell mass and insulin production. Although effective in maintaining euglycaemia, beta-cell compensation creates the damaging hyperinsulinaemic milieu. The development of hyperglycaemia and diabetes occurs in the setting of impairment in the ability of beta cells to compensate. Intact insulin signalling appears to be crucial to the beta cells' expansion. Impaired insulin signalling in the islet likely contributes to a suboptimal compensatory response, serving as an additional insulin accelerate progression to impaired glucose homeostasis.

**Ovarian dysfunction**

Polycystic ovarian syndrome (PCOS) is a common cause of reproductive dysfunction; menstrual irregularity and hyperandrogenism are hallmarks of the condition. Epidemiological studies support the relationship between obesity and PCOS, further evidenced by observations that modest weight loss can reduce the manifestations of the disease. Insulin resistance appears to be an important contributor to the pathogenesis of PCOS, mediating androgen secretion. Insulin resistant states other than those observed in obese individuals are associated with ovarian dysfunction that bears many of the hallmarks of PCOS. The severity of IR correlates to the degree of ovarian dysfunction, as is evidenced in monogenic disorders of IR that present with precocious puberty and polycystic ovaries. Menstrual irregularity and features of hyperandrogenism can often be the initial presentation of SIR syndromes.

**Cutaneous manifestations**

Acanthosis nigricans are cutaneous hyper-pigmented plaques that have a velvety appearance. It is usually present at skin folds: most commonly the axilla, flexor surfaces and neck fold. Pathogenesis in IR likely relates to the stimulation of dermal keratinocytes, fibroblasts and insulin-like growth factor (IGF) receptors by the hyperinsulinaemic state created in the setting of impaired insulin signalling, resulting in epidermal hyperplasia. Hereditary causes where genetic counselling improve insulin sensitivity, treat the metabolic complications and identify the manifestations of the disease. Epidemic hyperplasia, better known as skin tags, are another manifestation of IR. Most often occurring along the neck and flexures, they appear as pedunculated protrusions from the skin's surface. The number of acrochordons correlates closely with the severity of IR; however, its absence does not exclude the presence of IR. Acrochordons, better known as skin tags, are another manifestation of IR. Most often occurring along the neck and flexures, they appear as pedunculated protrusions from the skin’s surface. The number of acrochordons correlates closely with the degree of IR. The exact pathogenesis is undetermined but, as in the case of acanthosis nigricans, it may relate to IGF receptor stimulation.

**Dyslipidaemia**

Abnormal lipid profile is a common component of the IR phenotype; typically, hypertriglyceridaemia and low high-density lipoproteins (HDLs) are seen. The primary defect arises due to the hepatic production of triglyceride-rich very low-density lipoprotein (VLDL). Fatty acids act as a driver of VLDL production and there is increased flux of fatty acids into the liver in states of IR. In the resistant state, insulin fails to suppress lipolysis. In addition, endogenous hepatic fatty acid production increases in insulin resistant states and further contributes to the observed increases in VLDL. HDL levels are inversely related to IR; the latter appears to arise as a downstream consequence.
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of increased VLDL where the composition of HDL is altered due to the exchange of cholesterol esters and triglyceride. Apo AI is the predominant HDL apolipoprotein and exhibits increased renal clearance, and decreased circulating levels are present in IR. These lipid abnormalities are not seen in patients with insulin receptor defects, and this can be a useful diagnostic clue in the presence of other features of SIR.

Non-alcoholic fatty liver disease
A relationship between abdominal obesity and fatty liver has long been recognised. NAFLD commonly precedes the development of overt diabetes mellitus and raises the question: ‘what is the relationship between NAFLD and insulin resistance?’ It has been shown consistently in the literature that whole body, hepatic and adipose IR is strongly associated with hepatosteatosis. However, it is more challenging to prove causation and the contribution of IR in the development of hepatosteatosis has yet to be fully elucidated. Supporting the role of IR in the development of NAFLD has been the response of affected individuals to the insulin sensitising agent pioglitazone. NAFLD is not part of the phenotype of complete insulin receptoropathies, suggesting that a post-receptor insulin resistant defect contributes to the pathogenesis of both hepatosteatosis and dyslipidaemia. It is, however, consistently seen in obesity and lipodystrophies. As with absence of hypertriglyceridaemia, absence of NAFLD can be another clue to a diagnosis of insulin receptoropathy in patients with other features of SIR (Figure 1).

Disorders of IR relating to adipose tissue

Obesity
Obesity has become increasingly prevalent: over 25% of the UK population have a BMI >30kg/m². In parallel with increasing obesity rates, we have seen significant rises in the development of diabetes mellitus and NAFLD. Insulin resistance is strongly associated with obesity, and particularly abdominal obesity as measured by waist circumference.

However, there remains a subset of obese individuals who do not exhibit the classical IR phenotype outlined above and are in fact metabolically healthier than weight-matched counterparts. Among adults, adipocyte number remains stable and as this is the primary organ of lipid storage so too does our capacity to store excess energy as fat in adipocytes. Adipose mass can increase due to expansion of the lipid volume in the adipocyte; however, it appears that, once this capacity is exceeded, fat is retained in ectopic or non-adipose sites, in particular muscle and hepatic tissue. Ectopic fat storage and lipotoxicity associated with obesity become a mediator of post-receptor IR. Obesity and associated impairment in adipose tissue expandability remain the most common cause of IR in our clinics. Insulin resistance associated with obesity shares many of the clinical features of other less common causes of SIR including impaired glucose homeostasis, ovarian dysfunction, acanthosis nigricans, skin tags, NAFLD and dyslipidaemia. The presence of any of these features in an obese individual would prompt consideration for IR and investigation for the other associated features.

Lipodystrophy
Lipodystrophies represent a heterogeneous group of disorders with the common pathology of selective adipose tissue loss. As alluded to earlier, adipose tissue is an essential organ for its ability to efficiently store excess energy as lipid and communicate information regarding nutritional state to the central nervous system by the production of the hormone leptin. In lipodystrophies, the storage of excess energy as lipid in adipose tissue is impaired with the consequences of ectopic fat storage in liver, pancreas and muscle which induces IR. It is logical that the greater the degree of adipose tissue loss the more severe the limitations on the body’s capacity to buffer changes in fat and the more marked the metabolic consequences of ectopic fat storage. Lipodystrophies have been classified on the basis of whether the loss of adipose tissue is generalised or partial (Table 1). The causes of lipodystrophies vary from inherited conditions to acquired conditions that have a strong association with autoimmunity.

Congenital generalised lipodystrophy
Congenital generalised lipodystrophies (CGL) typically present at birth, and the inheritance of known monogenic disorders is autosomal recessive in

Figure 1. Clinical features of severe insulin resistance syndromes

*Also reported in partial insulin receptor signalling defect. **Diffs with extent of fat loss, typically normal in FPLD1 (familial partial lipodystrophy type 1). NAFLD = non-alcoholic fatty liver disease; IGFBP1 = insulin-like growth factor binding protein-1; SHBG = sex hormone binding globulin.
nature. The original syndrome described was Berardinelli-Seip syndrome which manifests a near total absence of subcutaneous adipose tissue; two candidate genes were identified: AGPAT2 and BACL2 which remain the most common causes. A number of other causative genes have been identified and despite subtle differences reduced adipose tissue remains central to the phenotype. Clinically affected individuals also demonstrate calf muscular hypertrophy and acanthosis nigricans. The metabolic phenotype is striking in CGL with secondary diabetes and hypertriglyceridaemia which present very early in life; this coupled with low leptin levels leads to hyperphagia, which further exacerbates the dyslipidaemia. Much work has been done to elucidate the mechanism of generalised adipose dysfunction in these disorders. Most mutant genes appear to impair the adipocyte’s ability to take up or synthesise lipid, i.e. AGPAT2, CAV1, PCTY1A and PTRF. The BACL2 mutation, however, appears to play a role in adipogenesis.

Familial partial lipodystrophy. Familial partial lipodystrophies generally present after childhood and affected individuals often first come to attention as adults in the diabetes or endocrinology clinic. Partial lipodystrophy implies that a certain amount of subcutaneous adipose tissue remains; reasons for selective fat loss are unclear. The distribution of fat leads to a clinical phenotype that correlates closely to the genetic cause.

FPLD1 or Köbberling syndrome is polygenic and highly penetrant. Subcutaneous fat is reduced in limbs and buttock but truncal and facial adipose deposits are spared; musculature in the limbs is usually well defined due to the paucity of subcutaneous fat. The metabolic consequences are more marked than BMI matched controls including IR, NAFLD and hypertriglyceridaemia. Consequently, other features of hyperinsulinaemia are often present: acanthosis nigricans, acrochordons and hyperandrogenism. The remaining familial partial lipodystrophies are monogenic disorders.

FPLD2 is sometimes referred to as Dunnigan syndrome and represents a dominantly inherited lamin A/C (LMNA) gene mutation. The phenotype is one of reduced subcutaneous adipose tissue in the limbs, buttock but truncal and facial adipose tissue remains central to the phenotype. Clinically affected individuals also demonstrate calf muscular hypertrophy and acanthosis nigricans. The metabolic phenotype is striking in CGL with secondary diabetes and hypertriglyceridaemia which present very early in life; this coupled with low leptin levels leads to hyperphagia, which further exacerbates the dyslipidaemia. Much work has been done to elucidate the mechanism of generalised adipose dysfunction in these disorders. Most mutant genes appear to impair the adipocyte’s ability to take up or synthesise lipid, i.e. AGPAT2, CAV1, PCTY1A and PTRF. The BACL2 mutation, however, appears to play a role in adipogenesis.

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Acquired partial lipodystrophy (Barraquer-Simons syndrome). Acquired lipodystrophies also range in severity from partial to focal lipodystrophy with no apparent metabolic sequelae to generalised adipose tissue loss. Partial lipodystrophy is a common presentation in HIV patients and it is believed that the use of antiretroviral drugs is the cause. From HIV-related lipodystrophy the most common acquired partial lipodystrophy seen by the insulin resistance is associated with low complement 3 (C3) levels. It is associated with a typical cephalocaudal loss of subcutaneous fat, sparing of the face, neck and visceral deposits. Defective protein leads to reduced triglyceride accumulation in droplets and reduced size; however, they are increased in number and lipolysis is increased. The proband had marked dyslipidaemia and IR. The latter three monogenic partial lipodystrophies have only been described in a handful of individuals. Diagnosis in females is more common than in men as the typical phenotype of fat loss and muscular prominence is more dramatic in females who ordinarily have more adipose stores than males.

Other genes have been implicated in partial lipodystrophy. AKT2 and PLIN1 are both autosomal dominant and typically have loss of subcutaneous adipose tissue from the extremities. The former gene encodes for a protein essential to downstream insulin signalling while the latter plays an essential role in the outer membrane of the lipid droplet regulating lipid storage and release. AKT2 plays an important role in lipid accumulation and possibly adipocyte differentiation. The phenotype of SIR and diabetes was present in the affected cases; total body fat was lower than predicted. CIDEC is a lipid droplet membrane protein; it is associated with lipodystrophy and it is autosomal recessive. It is associated with a diffuse loss of subcutaneous fat, sparing of the face, neck and visceral deposits. Defective protein leads to reduced triglyceride accumulation in droplets and reduced size; however, they are increased in number and lipolysis is increased. The proband had marked dyslipidaemia and IR. The latter three monogenic partial lipodystrophies have only been described in a handful of individuals. Diagnosis in females is more common than in men as the typical phenotype of fat loss and muscular prominence is more dramatic in females who ordinarily have more adipose stores than males.

Table 1. Classification of syndromes of severe insulin resistance

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<tr>
<th>Defects of insulin signalling</th>
<th>Generalised (impaired/absent insulin receptor signalling):</th>
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<tr>
<td>Insulin receptor antibodies</td>
<td>- Rabson-Mendenhall/Donohue syndrome, Type A insulin resistance</td>
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<tr>
<td>Insulin receptor mutations</td>
<td>- Type B insulin resistance</td>
</tr>
<tr>
<td>Acquired</td>
<td>- Partial (impaired signalling post-receptor)</td>
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Adipocyte tissues abnormalities

**Obesity**

**Lipodystrophy**

Inherited:
- Familial partial lipodystrophy
  - Polygenic (Köbberling syndrome)
  - Monogenic (LMNA, PPARG, AKT2, PLN1, CIDEC)
- Congenital generalised lipodystrophy
  - Monogenic (AGPAT2/BACL2, CAV1, PTRF, PCTY1A)

Acquired:
- Partial
  - HIV, C3 nephritic factor associated
- Generalised
  - Autoimmune disease and/or low C4
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C3 nephritic factor can be measured and functions to activate C3 convertase controlling the alternate complement pathway. Urinalysis and assessment of renal function are important to screen for renal involvement. There is a strong association between acquired lipodystrophy and autoimmune conditions, with systemic lupus erythematosus and dermatomyositis among those most commonly reported in the literature.

**Acquired generalised lipodystrophy.** Generalised acquired lipodystrophies are less common. Low C4 lipodystrophy is also reported in a syndrome of diffuse fat loss, chronic autoimmune hepatitis and haemolytic anaemia. This differs from the low C3 syndrome where activation of the alternate complement pathway is implicated: C4 appears to be consumed by activation of the classical complement pathways due to disordered immunoglobulin production. Although mechanistically interesting, it remains an uncommon cause of acquired generalised lipodystrophy. Most cases of acquired generalised lipodystrophy are idiopathic although there are strong associations with autoimmune conditions.

**Disorders of IR relating to insulin signalling**

Disorders of insulin receptor signalling are an uncommon cause of IR; however, their clinical features are often quite dramatic. Defects in insulin signalling bear many of the hallmarks of other forms of IR, obesity and lipodystrophy such as acanthosis nigricans, skin tags, hyperandrogenism, ovarian dysfunction in females and impaired glucose homeostasis. Insulin receptoropathies are broadly categorised into disorders causing complete defects in insulin receptor signalling or ones of the downstream insulin-signalling pathway where the effect is partial.

**Insulin receptor defects.** The best-known monogenic insulin receptoropathies are Donohue syndrome and Rabson-Mendenhall syndrome. Both present in infancy and childhood manifesting features of developmental delay mentally and physically with impaired linear growth, reduced muscle and adipose mass. The classical features of IR may be present such as acanthosis and hyperandrogenism presenting as precocious pubertal development. Hypoglycaemia, often postprandial, is also a recognised feature of insulin receptor defects. Both syndromes are caused by autosomal recessive mutations in the insulin receptor gene; however, numerous other mutations in the insulin receptor or regulators of insulin gene transcription have been described. Subtle differences in phenotypes exist but IR remains consistent. Less severe insulin receptor mutations commonly present post pubertally and when it presents during this period it is referred to as Type A insulin resistance. The marked hepatosteatosis and dyslipidaemia associated with other forms of IR are not present in complete insulin receptor signalling defects.

**Partial insulin receptor signalling defects.** Distal to the insulin receptor is an intracellular cascade that mediates the hormones’ actions. It was conceivable that defects in this cascade may manifest as impaired insulin signalling and to date a number

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**Figure 2. Diagnostic approach to severe insulin resistance syndrome**

Clinical suspicion of insulin resistance

(Ovarian dysfunction, acanthosis nigricans, skin tags, hepatosteatosis, dyslipidaemia, selective fat loss)

**Clinical suspicion of insulin resistance**

- Diabetes
  - ↑↑ Insulin doses
  - >3 u/kg
- Normoglycaemic
  - ↑ Fasting insulin
  - >150 pmol/L

**Insulin resistance**

(Check lipid profile, adiponectin)

- Adipose disorder
  - ↑↑ BMI
- Lipodystrophy
- Insulin receptor defect

**Specialist referral/genetic testing**

Fasting insulin (N)

- No insulin resistance
- ↑↑ BMI
- Fat loss

- Obesity
- Lipodystrophy
- Insulin receptor defect

- ↑↑ BMI
- Fat loss
- Adipose disorder

- TG ↑/HDL ↓
- ↓ adiponectin

- Adiponectin

- Fasting insulin (N)

- >150 pmol/L

- Insulin resistance

- Check lipid profile, adiponectin

- No insulin resistance
of post-receptor defects have been recognised. We have already mentioned one: an autosomal dominant mutation in the AKT2 gene – as well as presenting with features of IR reported cases have partial lipodystrophy.\(^2\) AKT2 has provided important mechanistic insight into the role of IR in NAFLD and dyslipidaemia. Complete insulin receptor mutations are free of the NAFLD and dyslipidaemic phenotype; however, it is present in AKT2 mutations. These findings support the role of post-receptor IR in the pathogenesis of non-alcoholic steatohepatitis and dyslipidaemia.\(^3\)

**Insulin receptor antibodies.** While Type A insulin resistance is a heterogeneous disorder due to defective insulin receptor activity, Type B insulin resistance represents a similar clinical syndrome; however, they are differentiated mechanically. In this condition insulin receptor function is impaired due to the presence of anti-insulin receptor antibodies leading to increased endogenous insulin secretion. This disorder often co-exists with other autoimmune conditions. Acanthosis nigricans, hyperandrogenism and hyperglycaemia are hallmarks of the condition.\(^5\) The onset is often abrupt, with weight loss, severe acanthosis nigricans and insulin requirements often in the thousands of units per day.

**Diagnosis and differentiation: how is ‘severe’ IR defined in clinical practice?** In defining IR in the research setting a hyperinsulinaemic euglycaemic clamp is often used, where the rate of glucose disposal in response to a fixed insulin infusion determines sensitivity to insulin.\(^6,7\) Although the gold standard, hyperinsulinaemic euglycaemic clamps are impractical in the clinical setting. Biochemical markers of IR based on single measurements offer a useful alternative to dynamic studies. In practice we most commonly consider SIR in the setting of diabetes where patients require large doses of exogenous insulin (>3units/kg) to control blood glucose levels. Insulin levels can be useful in the diagnosis of IR; however, their utility is limited in those who have developed beta-cell dysfunction.\(^8\) SIR can be defined by fasting insulin >150pmol/L, and/or OGTT 2 hour glucose >1500pmol/L. Some patients with SIR have partial beta-cell failure and in these a careful clinical history and examination are required, with attention to age of onset, family history and clinical examination findings of acanthosis nigricans and/or abnormalities and/or changes in adipose tissue topography.

Similarly, the homeostasis model assessment (HOMA) bases its quantification of insulin sensitivity on fasting measures of insulin and glucose. It is based on the principle that blood glucose concentrations are a product of beta-cell function and insulin sensitivity.\(^1,8\) HOMA-IR is a helpful single measurement for the assessment of IR; however, as with a single fasting insulin measurement it can be difficult to standardise testing procedures, which will impact on the validity of the result (HOMA is usually used in epidemiological studies rather than in individuals). An alternative to this is the leptin:adiponectin ratio which acts as a surrogate measure for insulin sensitivity and correlates closely to insulin clamp studies.\(^9\) To strengthen the validity of biochemical measurements a thorough clinical assessment detailing evidence of the patient’s phenotype is essential. Together, these tools allow the diagnosis of IR and differentiation between obesity-related IR, lipodystrophy and insulin receptoropathies. In the preceding paragraphs we have outlined features common to all IR syndromes and have outlined specific phenotypic characteristics that assist in differentiating the aetiology of IR (Figure 1). There are also additional biochemical clues. Adiponectin is a hormone derived from adipose tissue; it correlates closely to insulin sensitivity in vivo – however, the role of this adipokine remains unclear. In the case of IR related to obesity or lipodystrophy adiponectin levels are typically low. Complete insulin signalling defects are associated with adiponectin that is normal or elevated.\(^70\)

This is important mechanistically: it tells us that insulin receptor function is important in the regulation of adiponectin production and also allows us to differentiate between IR pathologies.

**Conclusion** Insulin resistance is prevalent in clinical practice; obesity remains the most common disease mediator. However, SIR and its accompanying metabolic complications may also present in the non-obese due to hereditary or acquired disorders many of which remain undiagnosed until end-organ complications have developed. Increased awareness of SIR syndromes will enable earlier diagnosis and intervention.

**Declaration of interests** There are no conflicts of interest declared.

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