Monogenic diabetes

Fotini K Kavvoura
Katharine R Owen

Abstract

Whereas most people with diabetes mellitus have type 1 (T1DM) or type 2 (T2DM) diabetes, there are a number of other inherited forms of diabetes and insulin resistance syndromes, which represent up to about 5% of all cases of diabetes. Monogenic forms of pancreatic β-cell dysfunction include maturity-onset diabetes of the young (MODY) and neonatal diabetes (NDM), with MODY being the most common form of inherited diabetes. The long-term response to sulfonylurea drugs in MODY caused by *HNF1A* and *HNF4A* mutations and NDM caused by *KCNJ11* and *ABCC8* mutations is an excellent example of pharmacogenetics. Mitochondrial diabetes is maternally inherited and usually associated with sensorineural deafness and other neurological features. Monogenic severe insulin resistance can be divided into adipose tissue defects (lipodystrophies, characterized by abnormal fat distribution) and disorders of insulin signalling. Molecular diagnosis of inherited diabetes has important implications for patients, allowing personalized management and screening of their relatives. Misclassification of monogenic diabetes or severe insulin resistance as T1DM and T2DM is common, and new tools for prioritizing suspected cases for genetic testing are needed.

Keywords Biomarkers; genetics; lipodystrophy; maturity-onset diabetes of the young (MODY); mitochondrial diabetes; monogenic diabetes; MRCP; neonatal diabetes; personalized medicine; severe insulin resistance

Key points

- Up to about 5% of cases of diabetes mellitus have a rare aetiology that is neither type 1 nor type 2
- Consider maturity-onset diabetes of the young in young adults who are β-cell antibody negative without insulin resistance or obesity
- All those diagnosed with diabetes before 1 year of age should be investigated for genetic causes of neonatal diabetes regardless of current age
- Consider genetic severe insulin resistance in those with young-onset metabolic syndrome or acanthosis nigricans without obesity, or if there is abnormality of body fat distribution
- Think about a unifying diagnosis in individuals with diabetes plus other clinical features
- Diagnosing a rare form of diabetes can change treatment, including discontinuing insulin, for example to use sulfonylurea drugs in diabetes caused by *HNF1A, HNF4A, ABCC8* and *KCNJ11* mutations
- Identifying a monogenic syndromic cause for diabetes allows screening and earlier detection of other conditions associated with the syndrome

Introduction

Diabetes mellitus is a group of diseases characterized by hyperglycaemia resulting from reduced insulin production, abnormal insulin action or both. Although most cases of diabetes can be categorized as either type 1 (T1DM) or type 2 (T2DM), there are many less common aetiologies, ranging from single-gene disorders to rare syndromes and acquired causes. This article covers the single-gene (monogenic) causes of pancreatic β-cell dysfunction and severe insulin resistance, concentrating on the clinical features and management of the forms most commonly encountered. Figure 1 shows a suggested diagnostic algorithm for diabetes diagnosed in young adulthood.

Maturity-onset diabetes of the young (MODY)

MODY is the general name for monogenic β-cell dysfunction and was described clinically in the pre-genomic era. The most common genes causing MODY were identified in the 1990s by studying large multigenerational families. MODY is characterized by:

- autosomal dominant inheritance
- young age of onset (often the second or third decade)
- absence of β-cell autoimmunity
- absence of features of metabolic syndrome
- sustained endogenous insulin production (C-peptide positivity).

MODY represents 1–6% of cases of diabetes[1,2] (with the highest prevalence in children and younger adults), but it is estimated that around 80% of cases are misclassified as T1DM or T2DM.[1] Molecular genetic diagnosis is available in most developed countries using either Sanger sequencing (UK cost at time of writing £350 per gene) or, increasingly, next-generation sequencing of panels of genes.

The implications of molecular diagnosis are important not only for the probands, by allowing personalized management, but also for their relatives, by prompting cascade screening and definitive diagnosis.

Fotini Kavvoura ***MD PhD MRCP*** *is a Consultant in Diabetes and Endocrinology at the Royal Berkshire Hospital, Reading, UK. She has an interest in the genetics of type 2 diabetes with a focus on young-onset diabetes, how genetic variation contributes to disease risk and how genetic profiling can aid clinical practice. Competing interests: none declared.*

Katharine Owen ***BSc MD FRCP*** *is an Associate Professor in the University of Oxford and Consultant Physician at the Oxford Centre for Diabetes, Endocrinology and Metabolism, UK. Her research interests involve understanding the genetic aetiology of diabetes in young adults, the identification and characterization of unusual kinds of diabetes, biomarkers for monogenic diabetes and management of rare forms of diabetes. Competing interests: none declared.*

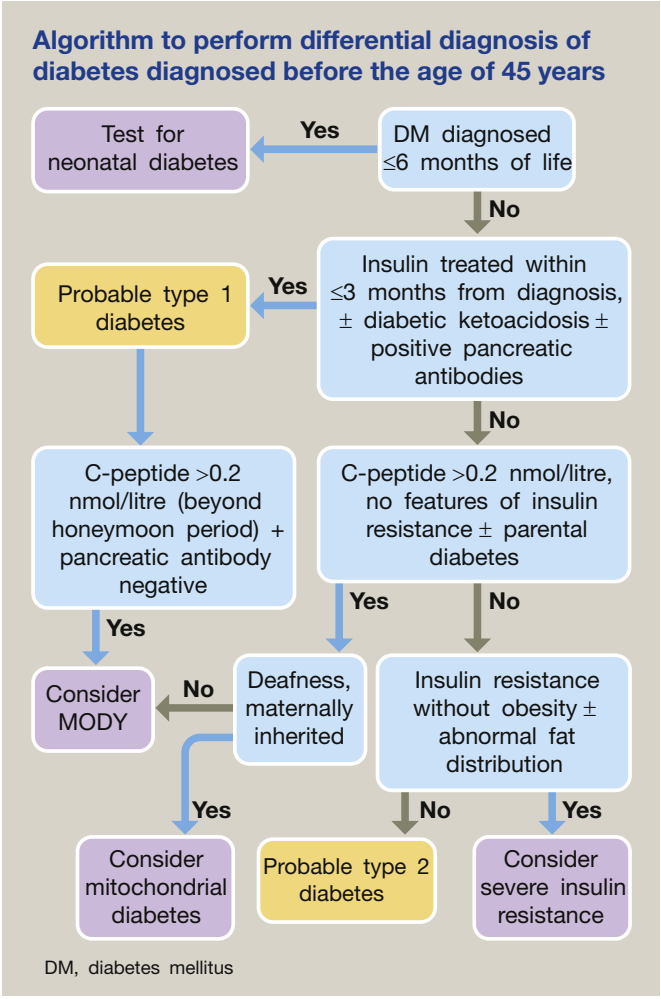

Figure 1

The most common types of MODY (in order of frequency in the UK) are caused by mutations in the hepatic nuclear factor 1α (*HNF1A*), glucokinase (*GCK*), hepatic nuclear factor 4α (*HNF4A*) and hepatic nuclear factor 1β (*HNF1B*) genes.[1]

GCK-MODY (previously MODY2)

Glucokinase (GCK), known as the pancreatic β-cell glucose sensor, is a key regulatory enzyme in glucose-stimulated insulin secretion. Heterozygous inactivating mutations raise the glucose threshold at which insulin secretion occurs, leading to mild, often subclinical, non-progressive, fasting hyperglycaemia (fasting plasma glucose 5.5–8.0 mmol/litre, glycated haemoglobin 5.8–7.6%, 40–60 mmol/mol), which is present from birth.

A unique feature of *GCK* mutations is that insulin secretion remains intact and regulated, albeit shifted 2–3 mmol/litre higher than normal. This results in low postprandial glucose excursions compared with other forms of diabetes. Patients do not develop microvascular complications, nor do they appear to have a higher risk of macrovascular complications than age-matched non-diabetic individuals, so treatment is not recommended outside pregnancy. In pregnancy, the baby's birthweight depends on whether the fetus is affected, so fetal growth should be monitored.

Diagnosis of GCK-MODY is often incidental and depends on the level of diabetes screening in the population. It accounts for 32% of all cases of MODY in the UK and may be identified for the first time during pregnancy.

HNF1A-MODY (previously MODY3)

This is the most common type of MODY, accounting for 52% of all cases in the UK. Heterozygous mutations in the transcription factor *HNF1A* cause progressive β-cell dysfunction, resulting in hyperglycaemia in the second to fourth decades of life. As in T1DM and T2DM, microvascular and macrovascular complications are common if glycaemic targets are not achieved, and specialist follow-up is recommended.

One of the most important features of HNF1A-MODY is sensitivity to sulfonylurea drugs. Low-dose sulfonylurea (e.g. gliclazide 20–40 mg daily) represents the first-line treatment and can usually be safely substituted in patients managed initially with other treatments, including insulin, with no deterioration in glycaemic control. Most patients, however, eventually require treatment escalation and eventually insulin as β-cell dysfunction progresses.

Extrapancreatic features of HNF1A-MODY include a low renal threshold for glucose and a low concentration of serum C-reactive protein (CRP), the latter having potential usefulness as a biomarker for HNF1A-MODY.

HNF4A-MODY (previously MODY1)

Mutations in *HNF4A* cause a similar phenotype to HNF1A-MODY but are less common (accounting for about 10% of MODY in the UK). One difference is that *HNF4A* mutations cause hyperinsulinaemia *in utero* and during the neonatal period, leading to macrosomia and neonatal hypoglycaemia. This is generally transient, progressing to normal glycaemia in childhood, and subsequently to diabetes. The cause is not fully understood. HNF4A-MODY can also be treated successfully with low doses of a sulfonylurea. Renal glucose threshold and CRP are normal.

HNF1B-MODY (previously MODY5)

Mutations in *HNF1B* lead to developmental anomalies of the pancreas, kidneys and genitourinary system, also termed 'renal cysts and diabetes syndrome'. HNF1B-MODY accounts for around 6% of cases of MODY in the UK. Renal abnormalities are evident from early gestational life and are frequently the first presentation. Non-diabetic renal failure can occur. Pancreatic atrophy leads to both diabetes and pancreatic exocrine insufficiency in adult life. In contrast to HNF1A-MODY, patients are not sensitive to sulfonylureas, and progress to insulin treatment relatively quickly.

Rarer types of MODY

Mutations in *KCNJ11*, *ABCC8* and *INS* cause up to 1% of MODY, but they are far better known for their role in neonatal diabetes mellitus (NDM; see below). Other genes e.g. *IPF1* (also known as *PDF1*), *NEUROD1*, *BLK*, *KLF11*, *CEL* have been implicated in MODY families but have each been reported in only a handful of cases, and the genetic evidence is not always compelling. These genes are not routinely screened for in diagnostic testing for MODY. In some families with autosomal dominant insulin-deficient diabetes, no causative gene has been identified, despite recent use of exome or whole-genome sequencing.

Mitochondrial diabetes

Mutations in the mitochondrial genome often cause diabetes.[3] The classic presentation is maternally inherited diabetes and deafness (MIDD), although these patients frequently have multisystem involvement including myopathy, other neurological symptoms and cardiac, renal and ophthalmic manifestations.

Clinical features overlap with T2DM and MODY. Oral agents can initially be successful, although metformin is relatively contraindicated because of the raised lactate levels often observed in mitochondrial disease. Progression to insulin is generally quick because of the relative insulinopenia. Patients are usually lean and insulin-sensitive. Diabetes arises in the third to fifth decade of life, but deafness often precedes it.

The most common mutation is the m.3243A>G point substitution, which also causes MELAS syndrome (mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes). Testing for this mutation is widely available, while sequencing of the whole mitochondrial genome is offered in more specialist centres. Specialist monitoring for other manifestations of mitochondrial disease is advised. Genetic counselling should be offered to female carriers as their children invariably inherit the mutation, but with unpredictable penetrance and clinical consequences.

Neonatal diabetes mellitus

Diabetes presenting in the first 6 months of life is unlikely to be T1DM, based on negative pancreatic antibodies and the presence of protective human leucocyte antigen. NDM is rare, affecting 1 in 90,000–260,000 births. Two distinct subgroups exist: transient neonatal diabetes (TNDM), which usually remits by 12 weeks of age but can relapse after some years, and permanent neonatal diabetes (PNDM). Mutations in any of around 30 genes have been associated with NDM, many associated with rare syndromes.

The most common causes of PNDM (40% of cases) are activating mutations in the *KCNJ11* and *ABCC8* genes, encoding the Kir6.2 and receptor 1 (SUR1) subunits, respectively, of the pancreatic β-cell K_{ATP} channel, leading to a reduction or lack of insulin secretion. Molecular diagnosis of this type of PNDM is important as it can be treated very successfully with high doses of sulfonylurea. Some K_{ATP} channel mutations cause the more severe syndrome of psychomotor developmental delay, epilepsy and neonatal diabetes (DEND). Insulin (*INS*) gene mutations are also common causes of PNDM (15% of cases); patients present with ketoacidosis and require life-long insulin treatment but have no syndromic features. Homozygous and compound heterozygous inactivating mutations of *GCK* are a rare cause of insulin-dependent PNDM.

In TNDM, the most common underlying mechanism is a methylation defect at chromosome 6q24 (*ZAC* and *HYMAI*). It usually presents in the first week of life and disappears by the 12th week. In half of cases, it recurs later in childhood. Insulin treatment is needed, but requirements gradually diminish. Mutations in *KCNJ11*, *ABCC8* and *INS* can also present as TNDM.

Understanding the wide monogenic aetiology of NDM has been a success story for molecular diagnostics.[4] Large collections of patients and a highly collaborative international approach has allowed a genetic diagnosis to be made in >80% of cases. Making a rapid diagnosis as soon as a baby presents with diabetes also allows screening and early diagnosis of other features in syndromic causes such as Wolcott–Rallison syndrome.

Inherited severe insulin resistance

Monogenic severe insulin resistance can be divided broadly into defects of adipose tissue (lipodystrophies) and disorders of insulin signalling.[5] Like MODY, the diagnosis is often missed and the true prevalence is unknown.

Lipodystrophies

Lipodystrophies are characterized by lack of adipose tissue that can be partial or generalized, with a genetic or acquired aetiology. There is limited capacity to store excess caloric intake as subcutaneous fat, so fat overflows into other organs such as the liver, pancreas and pericardium ('ectopic fat'). Examination of adipose distribution in an undressed patient is critical to timely diagnosis. Pathological absence of fat can be difficult to discriminate from healthy leanness in men and athletic women by inspection alone, so a low index of suspicion for lipodystrophy should be maintained in a young adult with diabetes and features of the metabolic syndrome who is non-obese or has a muscular appearance.

Partial lipodystrophy is most commonly caused by *LMNA* or *PPARG* mutations. Subcutaneous fat loss, characteristically from limb and gluteal depots, starts in the second decade and is more clinically apparent in women, along with prominent superficial veins. Preservation of fat in the face and neck of patients with *LMNA* mutations can lead to investigation for Cushing's syndrome. *PPARG* mutations commonly produce severe early-onset hypertension as well as lipodystrophy and other features of the metabolic syndrome. Many rarer causes of partial lipodystrophy exist, some lacking an established genetic aetiology.

Generalized lipodystrophy presents with absence of adipose tissue from birth. It is very rare and usually caused by recessive mutations in *AGPAT2* or *BSCL2*.

Disorders of insulin signalling

Inherited disorders of insulin signalling are mostly accounted for by insulin receptor (*INSR*) mutations, with a few rarer causes. Affected female patients usually present during puberty with features of polycystic ovary syndrome, acanthosis nigricans and (often) diabetes, while men commonly present with features of T2DM in later life. Very rare recessive childhood forms (Donohue or Rabson–Mendenhall syndromes) also exist. Interestingly, genetic defects in the *INSR* gene produce severe insulin resistance without dyslipidaemia or fatty liver. This, together with measurement of other serum markers such as adiponectin (which is raised in INSR mutations), allows their biochemical discrimination with a high degree of confidence before genetic testing.

Management of inherited severe insulin resistance

Treatment of severe insulin resistance can be very challenging. Careful attention to minimizing excess caloric and fat intake is critical in lipodystrophy even if body mass index (BMI) is normal. Bariatric surgery may be indicated. As for T2DM, metformin is the usual first-line treatment. The precise place of other oral therapies remains to be established. Stronger concentrations

Genetic syndromes associated with diabetes mellitus

Name	Genetic disorder	Inheritance	Clinical characteristics	Age at presentation of diabetes	Diabetes treatment
Obesity-related syndromes and diabetes					
Alström syndrome	*ALMS1* gene mutations	Autosomal recessive	Childhood obesity, congenital retinal dystrophy, sensorineural deafness, hypertriglyceridaemia, hyperinsulinaemia, early-onset T2DM	Childhood to early adulthood	Diet, oral agents, insulin
Laurence—Moon—Biedl syndrome	*BBS* genes (at least 14 genes) mutations	Autosomal recessive	Short stature, RP, learning and speech disabilities, ataxia, spastic paraplegia, renal abnormalities, DM	Childhood to early adulthood	Diet, oral agents, insulin
Bardet—Biedl syndrome			Obesity, RP, polydactyly, male hypogonadism, renal abnormalities, DM		
Prader—Willi syndrome	Chromosome 15q partial deletion	Paternally inherited	Hypotonia, low stature, learning disabilities, hyperphagia, obesity, neuropsychiatric disorders, T2DM	Childhood to early adulthood	Diet, oral agents, insulin
Chromosomal disorders and diabetes					
Down's syndrome	Trisomy of chromosome 21	Sporadic	Short stature, distinct facial characteristics, learning disabilities, congenital heart defects, autoimmune thyroid disorders, T1DM, coeliac disease	Early childhood to adulthood	Insulin
Klinefelter's syndrome	XXY males	Sporadic	Tall males with reduced musculature, gynaecomastia, hypogonadism Insulin resistance, metabolic syndrome, IGT in 40% of cases	Middle age	Diet, oral agents, insulin
Turner's syndrome	XO females	Sporadic, maternal germ cell XO mosaicism	Short stature, neck webbing, low-set ears, hypogonadism, congenital heart disease, hypothyroidism, diabetes, cognitive impairment	Adulthood	Diet, oral agents, insulin
Neurological conditions and diabetes					
Friedreich's ataxia	*FXN* gene mutations	Autosomal recessive	Muscle weakness, loss of coordination, staggering gait, scoliosis, cardiac, hearing and visual abnormalities, IGT 20% of cases, DM 10% of cases	Early adulthood	Diet, oral agents, insulin
Huntington's disease	*HTT* gene trinucleotide repeat disorder	Autosomal dominant	Choreoathetoid movements and neuropsychiatric problems, DM	Middle age	Diet, oral agents, insulin
Myotonic dystrophy	Type 1: *DMPK* gene trinucleotide disorder Type 2: *CNBP* gene trinucleotide repeat disorder	Autosomal dominant	Arrythmias, myotonia, insulin resistance, T2DM	Adulthood	Diet, oral agents, insulin
Exocrine pancreas disorders and diabetes					
Cystic fibrosis	*CFTR* gene mutations (ΔF508 most common)	Autosomal recessive	Recurrent chest infections, bronchiectasis, poor growth, malabsorption, male infertility, DM	Infancy to early adulthood	Insulin
Haemochromatosis	*HFE* gene mutations (C282Y and H63D most common)	Autosomal recessive	Iron overload leads to bronze/grey skin pigmentation, liver cirrhosis, hypogonadism, DM ('bronze diabetes'), heart arrhythmias, congestive heart failure, adrenal insufficiency, arthritis	Adulthood	Diet, oral agents, insulin
Other					
Wolfram syndrome type 1	*WFS1* gene mutations	Autosomal recessive	Diabetes insipidus, DM, optic atrophy, deafness = DIDMOAD		

DM, diabetes mellitus; IGT, impaired glucose tolerance; RP, retinitis pigmentosa.
Source: Adapted from the American Diabetes Association Diabetes and Classification of diabetes mellitus. *Diabetes Care* 2014 37(Supplement 1); S81-90.

Table 1

Useful online resources

Diapedia	www.diapedia.org	Open-access, peer-reviewed, unbiased and up-to-date knowledge base on all aspects of diabetes mellitus
DiabetesGenes, Exeter University, UK	www.diabetesgenes.org	Information for patients and professionals on research and clinical care in genetic types of diabetes, specifically MODY and NDM
National Center for Monogenic Diabetes at the University of Chicago, USA	http://monogenicdiabetes.uchicago.edu/	Online resource on monogenic diabetes for patients and health professionals
International Society for Pediatric and Adolescent Diabetes	www.ispad.org	Professional organization for those working with childhood and adolescent diabetes. Produces guidelines and educational resources
National Severe Insulin Resistance Service, Cambridge, UK	http://www.cuh.org.uk/addenbrookes-hospital/services/national-severe-insulin-resistance-service	Information on severe insulin resistance and lipodystrophy

Table 2

of insulin such as Humulin R 500 units/ml (a U500 isophane) or Toujeo (a U300 version of the analogue insulin glargine) can be useful in reducing the volume of insulin required. In lipodystrophy with a low leptin concentration, subcutaneous leptin treatment can be useful in improving metabolic complications. In the UK, leptin is available through the National Specialist Service for severe insulin resistance based in Cambridge. Aggressive cardiovascular risk management and careful screening for cirrhosis and its complications are also important.

Other genetic conditions often associated with diabetes

A comprehensive list of these conditions along with their underlying genetic cause is shown in Table 1, with an outline of the most common associated diabetes presentations. Although these are mostly rare, the association of diabetes with other clinical features should prompt consideration of a unifying diagnosis. Table 2 lists some useful online resources. ◆

KEY REFERENCES

1 Shields BM, Hicks S, Shepherd MH, Colclough K, Hattersley AT, Ellard S. Maturity-onset diabetes of the young (MODY): how many cases are we missing? *Diabetologia* 2010; **53:** 2504–8.

2 Johansson BB, Irgens HU, Molnes J, et al. Targeted next-generation sequencing reveals MODY in up to 6.5% of antibody-negative diabetes cases listed in the Norwegian Childhood Diabetes Registry. *Diabetologia* 2017; **60:** 625–35.

3 Murphy R, Turnbull DM, Walker M, Hattersley AT. Clinical features, diagnosis and management of maternally inherited diabetes and deafness (MIDD) associated with the 3243A>G mitochondrial point mutation. *Diabet Med* 2008; **25:** 383–99.

4 De Franco E, Flanagan SE, Houghton JA, et al. The effect of early, comprehensive genomic testing on clinical care in neonatal diabetes: an international cohort study. *Lancet* 2015; **386:** 957–63.

5 Parker VE, Savage DB, O'Rahilly S, Semple RK. Mechanistic insights into insulin resistance in the genetic era. *Diabet Med* 2011; **28:** 1476–86.

TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 20-year-old man presented with a 2-month history of tiredness and thirst. He had lost 2 kg in weight. His mother had type 1 diabetes mellitus, diagnosed at age 32 years after gestational diabetes 4 years previously.

On clinical examination, the man was well, with a body mass index of 21.4 kg/m^2. Blood ketones were not detected.

Investigations

- Fasting plasma glucose 8.1 mmol/litre (3.0–6.0)
- HbA_{1c} 73 mmol/mol (20–42), 8.8% (4.0–6.0)

What is the next most appropriate management action?

A Start basal bolus insulin and list for a carbohydrate-counting course

B Check β-cell antibodies, perform blood glucose and ketone monitoring and reassess in 2 weeks

C Start on metformin and refer to a community education group

D Start gliclazide and refer for genetic testing

E Reassure the patient that he does not need treatment

Question 2

A 28-year-old woman presented for pre-conception advice. She had had a diagnosis of type 2 diabetes mellitus for 2 years and was taking metformin and gliclazide. She had a family history of cardiomyopathy in her mother.

On clinical examination, she was wearing bilateral hearing aids and her body mass index was 23 kg/m^2.

Investigation

- HbA_{1c} 55 mmol/mol (20–42), 7.2% (4.0–6.0)

What's the most likely diagnosis?

A. maturity-onset diabetes of the young (MODY) due to *HNF4A* mutation
B. Wolfram syndrome
C. Mitochondrial diabetes
D. Type 1 diabetes
E. Mutation in the K_{ATP} channel

Question 3

A 16-year-old woman presented with clinical features of polycystic ovary syndrome.

On clinical examination, she had moderate hirsutism, a body mass index of 18.7 kg/m^2 and acanthosis nigricans in the neck and axilla.

Investigations

- Fasting plasma glucose 15 mmol/litre (3.0–6.0)
- Serum cholesterol 4.8 mmol/litre (<5.2)
- Serum low-density lipoprotein cholesterol 2.9 mmol/litre (<3.36)
- Serum total bilirubin 17 micromol/litre (1–22)
- Serum alanine aminotransferase 30 U/litre (5–35)
- Serum aspartate aminotransferase 21 U/litre (1–31)
- Serum alkaline phosphatase 89 U/litre (45–105)
- Testosterone 6.4 nmol/litre (0.5–3.0)
- Fasting insulin 650 pmol/litre (<186)

What is the most likely overarching diagnosis?

A. Polycystic ovary syndrome
B. Glucokinase MODY
C. Virilizing tumour of the ovary
D. Severe insulin resistance caused by insulin receptor mutation
E. Partial lipodystrophy caused by *PPARG* mutation