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The diagnosis and management of monogenic diabetes in children

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Definition

Monogenic diabetes results from the inheritance of mutation or mutations in a single gene. It may be dominantly or recessively inherited or may be a *de novo* mutation and, hence, a spontaneous case. In children, almost all monogenic diabetes results from mutations in genes that regulate β -cell function, although diabetes can rarely occur from mutations resulting in very severe insulin resistance (C) (1).

Diagnosis

Why diagnose monogenic diabetes?

The majority of patients with genetically proven monogenic diabetes are initially incorrectly diagnosed as having type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM) (2) (C). It is important to correctly diagnose monogenic diabetes as it can predict the clinical course of the patient, explain other associated clinical features, and, very important, guide the most appropriate treatment. In addition, making a diagnosis will have implications for other family members often correcting the diagnosis and treatment for other diabetic family members, as well as allowing appropriate genetic counseling.

Clinical presentation of monogenic diabetes

Clinical presentations in children when a diagnosis of monogenic diabetes should be considered are discussed below and include the following:

- (i) Neonatal diabetes and diabetes diagnosed within the first 6 months of life.
- (ii) Familial diabetes with an affected parent.
- (iii) Mild (5.5–8.5 mmol/L) fasting hyperglycemia, especially if young or familial.
- (iv) Diabetes associated with extra pancreatic features.

When to suspect a diagnosis of T1DM in children may not be correct?

Features in children initially thought to have T1DM that should suggest a possible diagnosis of monogenic diabetes are shown below. None of these are absolute and should be considered as together, rather than in isolation (C) (3).

- (i) A diagnosis of diabetes before 6 months (B) [in T1DM: <1% (4)].
- (ii) Family history of diabetes with a parent affected (C) [in T1DM: 2–4% (5)].
- (iii) Evidence of endogenous insulin production outside the 'honeymoon' phase (after 3 yr of diabetes), with detectable C-peptide (>200 nmol/L) when glucose level is >8 mmol/L (E) (in T1DM: 1–5%).
- (iv) When pancreatic islet autoantibodies are absent, especially if measured at diagnosis (C) [in T1DM: 3–30% (6–8)]. The great variation in antibody prevalence in series probably represents differences in assays and means it is hard to apply published series directly into clinical practice. Absent antibodies should lead to other investigation/consideration rather than leading directly to genetic tests (E).

When to suspect a diagnosis of T2DM in children may not be correct?

Features in children initially thought to have T2DM that should suggest a possible diagnosis of monogenic diabetes are shown below. It should be noted that most T2DM in youth will meet the former classification for maturity-onset diabetes of the young (MODY) [diagnosed <25, autosomal dominant inheritance and non-insulin dependent (C) (9–12)].

- (i) Not markedly obese or diabetic family members who are of normal weight [in T2DM: 20% (12)].

- (ii) Acanthosis nigricans not detected [in T2DM: 10% (9)].
- (iii) Ethnic background with a low prevalence of T2DM, e.g., European Caucasian (in T2DM: 0–45%).
- (iv) No evidence of insulin resistance with fasting C-peptide within the normal range [in T2DM: 0–20% (9–12)].

Making a diagnosis of monogenic diabetes

As well as having clinical features that are unusual for T1DM and T2DM, a patient on whom a diagnosis of monogenic diabetes is made should also have the features of a specific genetic subtype of monogenic diabetes (E). The features of the more common monogenic diabetes are given below.

While in T1DM and T2DM diabetes there is no single diagnostic test, this is not the case in monogenic diabetes where in >80% of cases, a molecular genetic diagnosis can be made by DNA testing (C). Molecular genetic testing is offered in most European countries and the USA, but many labs will test patients from other countries (for example, www.diabetesgenes.org and www.mody.no). These tests are expensive (up to €500/\$600) but can have a big impact on management of the proband and other family members, for whom it will be cheaper, as the mutation is known (€100/\$120). Some recently described monogenic diabetes genes like Kir6.2 testing in patients diagnosed less than 6 months may be available as research tests for no charge (see www.diabetesgenes.org). Approval from the patient's insurance company should be sought prior to sending DNA when applicable.

Given the limited resources available, it is vital that these tests are used in situations where they are likely to be positive and will alter clinical care. This will involve careful clinical selection and performing physiological tests like C-peptide and autoantibody measurement, as well as testing other family members before performing molecular genetic tests (E).

Specific subtypes of monogenic diabetes and their management

Neonatal diabetes and diabetes diagnosed within the first 6 months of life

There is good evidence that diabetes diagnosed in the first 6 months is not T1DM, as autoantibodies are rare and human leukocyte antigen (HLA) genotyping shows HLA haplotypes actually protective for T1DM in these patients (B) (4). Neonatal diabetes is another area which has rapidly moved from a clinical to a molecular genetic classification (13, 14). Neonatal diabetes is insulin-requiring diabetes, which is usually

diagnosed in the first 3 months of life. Clinically, two subgroups have been recognized: transient neonatal diabetes mellitus (TNDM) that resolved at a median of 12 wk and then did not require any treatment, although as many as 50% of cases would ultimately relapse (B) (15, 16); in contrast to permanent neonatal diabetes mellitus (PNDM), which required continual insulin treatment from diagnosis onward. For most patients with both types of neonatal diabetes, the molecular etiology can now be defined. The majority of patients with TNDM have an abnormality of imprinting of the *ZAC* and *HYMAI* genes on chromosome 6q (B) (14, 15), while the most common known cause of PNDM are mutations in the *KCNJ11* gene encoding the Kir6.2 subunit of the β -cell K_{ATP} channel (B) (17, 18). However, TNDM and PNDM are found with activating mutations in *KCNJ11* (Kir 6.2) and *ABCC8* [sulfonylurea receptor (SUR) 1]; some of these are amenable to treatment with sulfonylurea drugs which stimulate endogenous insulin secretion (19). If both parents are glucose intolerant, homozygous or compound heterozygous mutations in glucokinase are most frequent (20, 21).

Differential diagnosis. When diabetes is diagnosed in the neonatal period, it is difficult to tell if it is likely to be transient or permanent, although the features in Table 1 can help differentiate the possible different subtypes and can be used to guide molecular genetic testing.

TNDM from imprinting anomalies on 6q24. Imprinted anomalies of the 6q24 locus involving the *ZAC* and *HYAMI* genes are the most common cause of neonatal diabetes and result in TNDM (B) (14, 15, 22). The commonest 6q24 anomalies are inherited paternal duplications or paternal uniparental disomy, although methylation anomalies are being more frequently identified (E) (16). Diabetes associated with this is typically diagnosed within the first week and resolves around 12 wk (B) (15). In approximately 50% of cases, diabetes will reoccur during the pediatric age range (B) (15). Apart from macroglossia, seen in 23%, there are no non-pancreatic features (B) (15).

Initial glucose values can be very high (range: 12–57 mmol/L) and, therefore, insulin is used initially, although the dose can rapidly be reduced. Once patients have relapsed, they should remain under annual follow up due to the risk of diabetes relapsing. On relapse, patients are not insulin dependent and can be treated with diet initially, although subsequently, they often need insulin (E) (14). The response to oral treatments such as sulfonylureas or metformin is uncertain.

PNDM, TNDM and diabetes diagnosed in the first 6 months of life due to Kir6.2 mutations. Kir6.2 mutations are the second most common cause of

Table 1. Characteristics of diabetes presenting in the first 6 months of life [modified from reference (13)]

Gene, clinical syndrome, inheritance	PNDM/TNDM	Number of cases described (% in consanguineous or isolated populations)	Median birth weight in grams (SDS)	Age of diagnosis in weeks, median (range)	Pancreatic appearance	Other features
ZAC/HYAMI, imprinting defect on 6q24	TNDM	≈150, rare	2100 (-2.94)	0.5 (0-4)	Normal	Macroglossia (23%)
Kir6.2 (KCNJ11), spontaneous dominant (10%)	PNDM, TNDM (10%)	≈100, rare	2.580 (-1.73)	6 (0-260)	Normal	Developmental delay (20%), epilepsy (6%), DKA (30%)
EIF2AK3, Wolcott-Rallison syndrome, recessive	PNDM	30 (90)	?	13 (6-65)	Atrophy of pancreas (?), exocrine dysfunction (25%)	Epiphyseal dysplasia (90%), osteopenia (50%), acute liver failure (75%), developmental delay (80%), hypothyroidism (25%)
FOXP3, IPEX syndrome, X linked	PNDM	14, rare	2860 (-1.2)	6 (0-30)	?	Only boys affected, chronic diarrhea with villous atrophy (95%); pancreatic and thyroid autoantibodies (75%); thyroiditis (20%), eczema (50%); anemia (30%) and often die young (1 yr)
GCK (glucokinase), recessive	PNDM	6 (85)	1720 (-2.75)		Normal	Parents have fasting hyperglycemia, as heterozygotes
IPF1, recessive	PNDM	2 (50)	2140 (-2.97)		Absent	Parents may have early-onset diabetes, as heterozygotes
HNF-1β, dominant (60%) spontaneous	TNDM	2, rare	1900 (-3.21)		Atrophy	Renal developmental disorders
PTF1A, recessive	PNDM	3 (100)	1390 (-3.8)		Atrophy	Severe neurological dysfunction and cerebellar hypoplasia

DKA, diabetic ketoacidosis; HNF, hepatocyte nuclear factor; IPEX, immunodysregulation, polyendocrinopathy, enteropathy, X-linked; IPF1, insulin promoter factor 1; PNDM, permanent neonatal diabetes mellitus; SDS, standard deviation score; TNDM, transient neonatal diabetes mellitus.

mutations in patients with diabetes diagnosed in the first 6 months of life (B) (17, 18). While some (10%) have a remitting form of diabetes that may later relapse, the majority have PNDM (C) (23). Most patients have isolated diabetes, although neurological features are seen in 20% of patients. Despite being a heterozygous mutation, most have no family history, as 90% of cases are spontaneous mutations. The most severe defect is very marked developmental delay of motor and social function and generalized epilepsy often with hypsarrhythmia, as seen in West syndrome (C) (17). This has been called the developmental delay, epilepsy, and neonatal diabetes (DEND) syndrome (18). More common is the intermediate DEND syndrome where patients have less severe developmental delay and do not have epilepsy (18).

Patients with Kir6.2 mutations have all the clinical features of insulin dependency, as 30% of them present with ketoacidosis, and they usually do not have detectable C-peptide and, thus, are treated with insulin (C) (18). It has recently been shown that these patients can not only be successfully treated with oral sulfonylureas but can also get better glycemic control without an increase in hypoglycemia. The doses needed are high when calculated on a per kg body weight basis compared with adults, with patients typically needing 0.5 mg/kg/glibenclamide/d, although some may need as much as 1 mg/kg/d (C) (24–29). With time, many patients have been able to reduce their doses of sulfonylureas but maintain excellent glycemic control (E).

Wolcott–Rallison syndrome. Wolcott–Rallison syndrome is a rare autosomal recessive condition characterized by early-onset diabetes, epiphyseal dysplasia, renal impairment, acute hepatic failure,

and developmental delay (B) (30, 31). It is associated with mutations in *EIF2AK3* (32). Diabetes usually presents in infancy but may appear later. It is associated with β -cell loss, leading to insulin deficiency without autoimmune pathology. Insulin treatment is required. Wolcott–Rallison syndrome should be considered in any patient with diabetes in the first 3 yr who has epiphyseal dysplasia or acute severe hepatic failure (C, E) (30).

Other causes of neonatal diabetes. In Table 1, the clinical features of other causes of neonatal diabetes are outlined. Scanning the pancreas to assess if it is present and its size, checking for exocrine pancreatic function and pancreatic autoantibodies [found in the immunodysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome] are the most useful diagnostic tests before proceeding to molecular genetic testing (E). All other causes need to be treated with insulin. Some pediatricians consider that these patients are easiest to manage on subcutaneous insulin pumps. In patients with pancreatic aplasia, exocrine pancreatic supplements will be required.

Familial diabetes

The most common causes of familial diabetes or familial hyperglycemia are shown in Table 2.

Children and young adults with diabetes and a strong family history of diabetes: hepatocyte nuclear factor 1 alpha gene mutations (MODY3). The possibility of monogenic diabetes should be considered whenever a parent has diabetes, even if he/she is thought to have T1DM or T2DM (E). The most common form of monogenic diabetes which results in familial diabetes (known in the past as MODY) are hepatocyte nuclear

Table 2. Characteristics of common forms of monogenic diabetes and hyperglycemia

	Inheritance	Number of families identified in UK	Typical age of presentation in pediatric clinic (range)	Typical glucose level at presentation (range) mmol/L	Other clinical features
HNF-1 α (MODY3)	Dominant	197	14 (4–18)	17 (11–26)	Large increment in an OGTT (at 2–0 h usually >5 mmol/L), low renal threshold, progressive hyperglycemia with age, sensitive to sulfonylureas
HNF-4 α (MODY1)	Dominant	22	17 (5–18)	15 (9–20)	Similar to HNF-1 α but renal threshold normal
Glucokinase (MODY2)	Dominant (may not be diagnosed in parents as mild)	152	10 (0–18)	11 (5.5–16)	Usually incidental finding at diagnosis, fasting glucose in the range of 5.5–8 mmol/L, small increment in an OGTT (at 2–0 h usually <3.5 mmol/L), little deterioration in glycemia with age

HNF, hepatocyte nuclear factor; MODY, maturity-onset diabetes of the young; OGTT, oral glucose tolerance test.

factor (HNF)-1 α mutations (B) (33). The clinical characteristics of patients with HNF-1 α mutations are as follows:

- (i) Young-onset diabetes that shows characteristics of not being insulin dependent, e.g., not developing ketoacidosis in the absence of insulin, good glycemic control on a small dose of insulin, or detectable C-peptide measured when on insulin, with glucose >8 mmol/L outside a normally expected honeymoon period (3 yr) (E).
- (ii) Family history of diabetes. This may be treated with insulin and considered to be 'T1DM'. This would typically be diagnosed in the age of 20, 30, or 40 yr. There may also be an affected grandparent although often they are diagnosed after 45 yr (C).
- (iii) Oral glucose tolerance tests (OGTTs) in early stages tend to show a very large glucose increment, usually >5 mmol/L (34). Some subjects may have a normal fasting value but still rise into the diabetic range at 2 h (34) (B).
- (iv) Glycosuria at relatively normal blood glucose levels is often seen, as these patients have a low renal threshold (B) (34).
- (v) Marked sensitivity to sulfonylureas resulting in hypoglycemia, despite poor glycemic control before starting sulfonylureas (C) (35, 36).

Treatment. Patients with HNF-1 α gene mutations can initially be treated with diet although they will have marked postprandial hyperglycemia following a high carbohydrate meal, as the β -cell defect results in insufficient increase in insulin secretion with hyperglycemia (37).

Most patients will need pharmacological treatment, as they show progressive deterioration in glycemic control throughout life and are at risk of considerable microvascular and macrovascular complications (B,C) (38).

The first treatment to be used in children who are not controlled on insulin should be low-dose sulfonylureas, which results in a four-fold greater lowering of glucose than metformin (A) (39). These patients are extremely sensitive to sulfonylureas, and as long as they do not have problems with hypoglycemia, they can be maintained on these for many decades (C) (35). Glycemic control by sulfonylureas is often better than that achieved by insulin, especially in children and young adults (40). The dose of sulfonylureas should initially be low (one-quarter of the normal starting dose in adults) to avoid hypoglycemia (E). If there is hypoglycemia despite dose titration of a once- or twice-daily sulfonylurea preparation such as gliclazide, a slow-release preparation or meal time doses with a short-acting agent like nateglinide may be considered (C) (41).

Children and young adults with diabetes and a strong family history of diabetes: HNF-4 α gene mutations

(*MODY1*). Diabetes due to mutations of the HNF-4 α gene are considerably less common (Table 2) than diabetes due to mutations of the HNF-1 α gene but has similar characteristics, except that there is no low renal threshold and the age of diagnosis may be later (C) (42). HNF-4 α mutations should be considered when HNF-1 α sequencing is negative but the clinical features were strongly suggestive of HNF-1 α (42). Patients are often sensitive to sulfonylureas (C) (43).

Other causes of familial diabetes. A handful of families with autosomal dominant non-insulin-dependent diabetes have been described with mutations in insulin promoter factor 1 (*IPF1*) (*MODY4*) (44), *NeuroD1* (*MODY6*) (45, 46) and, recently, the carboxyl ester lipase (*CEL*) gene (*MODY7*) (47), but these are so unusual, they do not need to be tested for in children with diabetes except in a research setting (E) or when there are additional phenotypes, such as pancreatic exocrine dysfunction (47).

Mild fasting hyperglycemia: due to glucokinase mutations (*MODY2*)

The finding of raised fasting blood glucose in the range of 5.5–8.5 mmol/L is unusual in children and young adults. This always raises concern that they may be about to develop T1DM or that the patient has T2DM. However, a considerable proportion of these patients with persistent mild fasting hyperglycemia will have a heterozygous mutation in the glucokinase gene. The phenotype associated with glucokinase mutations is remarkably similar for all mutations. The following features suggest a diagnosis of a glucokinase mutation:

- (i) The fasting hyperglycemia is persistent and stable over a period of months or years (34).
- (ii) Hemoglobin A1c is typically just below or just above the upper limit of normal range (5.5–5.7%).
- (iii) In an OGTT, the increment (2-h glucose – fasting glucose) is small (typically <3.5 mmol/L), although because of the variability of the OGTT, this should not be considered an absolute criterion (34).
- (iv) Parents may have 'T2DM' or may not be diabetic. *On testing*, one parent will have a mildly raised fasting blood glucose, in the range of 5.5–8.5 mmol/L, as this is an autosomal dominant condition (C) (34). Testing of apparently unaffected parents' fasting glucose is important when considering a diagnosis of a glucokinase mutation (E).

Treatment. The fasting hyperglycemia does not deteriorate significantly and the glucose is regulated at the higher set point (34). This is rarely associated with

any microvascular or macrovascular complications even when no treatment is given throughout life (C) (48).

An important point is that these patients do not need treating in the pediatric age range. There is very little, if any, response to either oral hypoglycemic agents or insulin (E). Exogenous insulin results in reduction of endogenous insulin secretion and so the degree of glycemia will be maintained, explaining why these children can be treated with insulin without significant hypoglycemia.

Genetic syndromes associated with diabetes

When diabetes in a child is associated with other multi-system disease, the possibility of a monogenic syndrome that explains all features should be considered.

The Online Mendelian Inheritance in Man (OMIM) website [access via the National Center for Biotechnology Information (NCBI) website, <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi>] can help with clinical features and enables one to know if the gene has been defined and, hence, molecular genetic testing is available. For described and previously undescribed syndromes, assistance can be obtained through the International Society for Pediatric and Adolescent Diabetes (ISPAD) rare diabetes collection (access via the link on the ISPAD web page or through www.diabetesgenes.org). The most common genetic syndromes which include diabetes are listed below:

Diabetes insipidus, diabetes mellitus, optic atrophy, deafness syndrome (Wolfram syndrome). Wolfram syndrome is an autosomal recessive syndrome in which the association of diabetes with progressive optic atrophy under 16 yr of age is diagnostic (49). The syndrome is more common in countries where consanguineous marriages are frequent. Other features are bilateral sensorineural deafness, diabetes insipidus, dilated renal tracts, and truncal ataxia or more protean neurological signs, with the complete phenotype seen in 75% of patients, with increasing prevalence with age. The order of appearance of the neurological symptoms may vary even within families. The median age of death in Wolfram syndrome is 30 yr (49). Mutations in the gene for Wolfram syndrome (*WFS1*) are present in at least 90% of patients with clinical Wolfram syndrome (50–52).

The diabetes is non-autoimmune, insulin deficient, and presents at a mean age of 6 yr (49). Patients require insulin treatment from the time of diagnosis, but autoantibodies are not present (C) (49).

Thiamine-responsive megaloblastic anemia (Roger's syndrome). Thiamine-responsive megaloblastic anemia is a rare, recessive genetic syndrome of early-onset megaloblastic anemia (which responds to thiamine), and it is associated with diabetes and sensorineural deafness. This results from mutations in the gene *SLC19A2* (53).

The diabetes, which is insulin deficient in nature, is responsive to thiamine in some patients, although all seem to develop an insulin requirement in the long term (C) (54). Deafness is unresponsive to thiamine.

Renal cysts and diabetes syndrome due to a HNF-1 β mutation. Although initially described as a subgroup of familial diabetes (MODY5), it is now clear that patients with mutations in HNF-1 β rarely present with isolated diabetes (55). Renal developmental disorders, especially renal cysts and renal dysplasia, are present in almost all patients with mutations or gene deletions (56). They may be diagnosed *in utero* and precede the diagnosis of diabetes (B). Other features which may be present in children include uterine and genitalia developmental anomalies, hyperuricemia, gout, and abnormal liver function tests (55). A diagnosis of HNF-1 β should be considered in any child with diabetes who also has non-diabetic renal disease.

Patients with HNF-1 β mutations, unlike patients with HNF-1 α mutations, are not sensitive to sulfonylureas and, therefore, usually require insulin treatment (57). Pancreatic size is reduced, reflecting a reduction in both the endocrine and exocrine pancreas, and subclinical exocrine deficiency is present in most patients (58), but it is uncertain if this should be treated if it is asymptomatic.

Mitochondrial diabetes. Maternal transmission of mutated or deleted mitochondrial DNA can result in maternally inherited diabetes, although they are not usually in the pediatric age range. Despite that several mutations and deletions have been implicated, the strongest evidence relates to a point substitution at nucleotide position 3243 (A–G) in the mitochondrial tRNA [leu (UUR)] gene (B) (59). An identical mutation occurs in the mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like syndrome, and there may be some overlap between these syndromes in family members. Mitochondrial diabetes is commonly associated with sensorineural deafness and short stature. The diabetes is characterized by progressive non-autoimmune β -cell failure and may progress to needing insulin treatment rapidly.

Insulin-resistance syndromes: type A insulin resistance, leprechaunism, Rabson–Mendenhall syndrome and lipodystrophy. The key features of all insulin-resistance syndromes are acanthosis nigricans, androgen excess, and massively raised insulin concentrations in the absence of obesity (1). The more severe the insulin resistance and the earlier the onset, the more likely is diabetes (C) (1). A summary of some of the key clinical features is shown below [adapted from Musso et al. (1)] in Table 3.

Treatment of severe insulin resistance is very difficult. Most patients with diabetes have poor glycemic control and frequently develop long-term

Table 3. Characteristics of common insulin-resistance syndromes

Syndrome	Onset	Clinical features	Acanthosis nigricans	Androgen excess and hypertrichosis	Insulin levels	Gene involved
Leprechaunism	Congenital	Abnormal facies, large genitalia, small for gestational age, and growth retardation; rarely survive infancy	Yes – marked	↑↑↑, PCOS	↑↑↑	Insulin receptor, usually recessive
Rabson–Mendenhall	Congenital	Extreme growth retardation, abnormal dentition	Yes – marked	↑↑, PCOS	↑↑↑	Insulin receptor, usually recessive
Type A	Adolescence	Insulin resistance in absence of obesity	Yes – marked	↑↑↑, PCOS	↑↑↑	Insulin receptor, usually recessive
Lipodystrophy	Congenital or adolescence	Loss of subcutaneous fat – partial or total	Yes – may be marked	↑↑, PCOS +/-	↑↑	Total: seipin and AGPAT2 (recessive); partial: lamin AC and PPARG (dominant)

PCOS, polycystic ovarian syndrome.

complications(C) (1). Approaches used include the use of the insulin sensitizers, metformin, and glitazones, but their impact is limited when the insulin resistance is very severe. Insulin is the main stay of treatment, and 500 U insulin and insulin pumps are usually required (1). In partial lipodystrophy, metformin may have benefit and insulin is not required in the early stages (C) (60). In total lipodystrophy, the response of diabetes to recombinant lipodystrophy (61) can be dramatic but is only available on a research basis.

Recommendations

Advances in molecular genetics have led to the identification of the genes associated with many clinically identified subgroups of diabetes. The identification of genes has explained clinical heterogeneity in conditions defined on the basis of when they were diagnosed, e.g., neonatal diabetes and MODY. Now molecular genetics is being used as a diagnostic test which can help define the diagnosis and treatment of children with diabetes. As these tests are expensive, genetic testing should be limited to those who on clinical grounds are likely to be positive (E).

This article is a Chapter in the ISPAD Clinical Practice Consensus Guidelines 2006–2007 of the International society for pediatric and Adolescent diabetes (ISPAD, www.ispad.org). The complete set of these Guidelines will later be published as a compendium. Additional comments, clarifications or corrections should be directed to the Corresponding Author.

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