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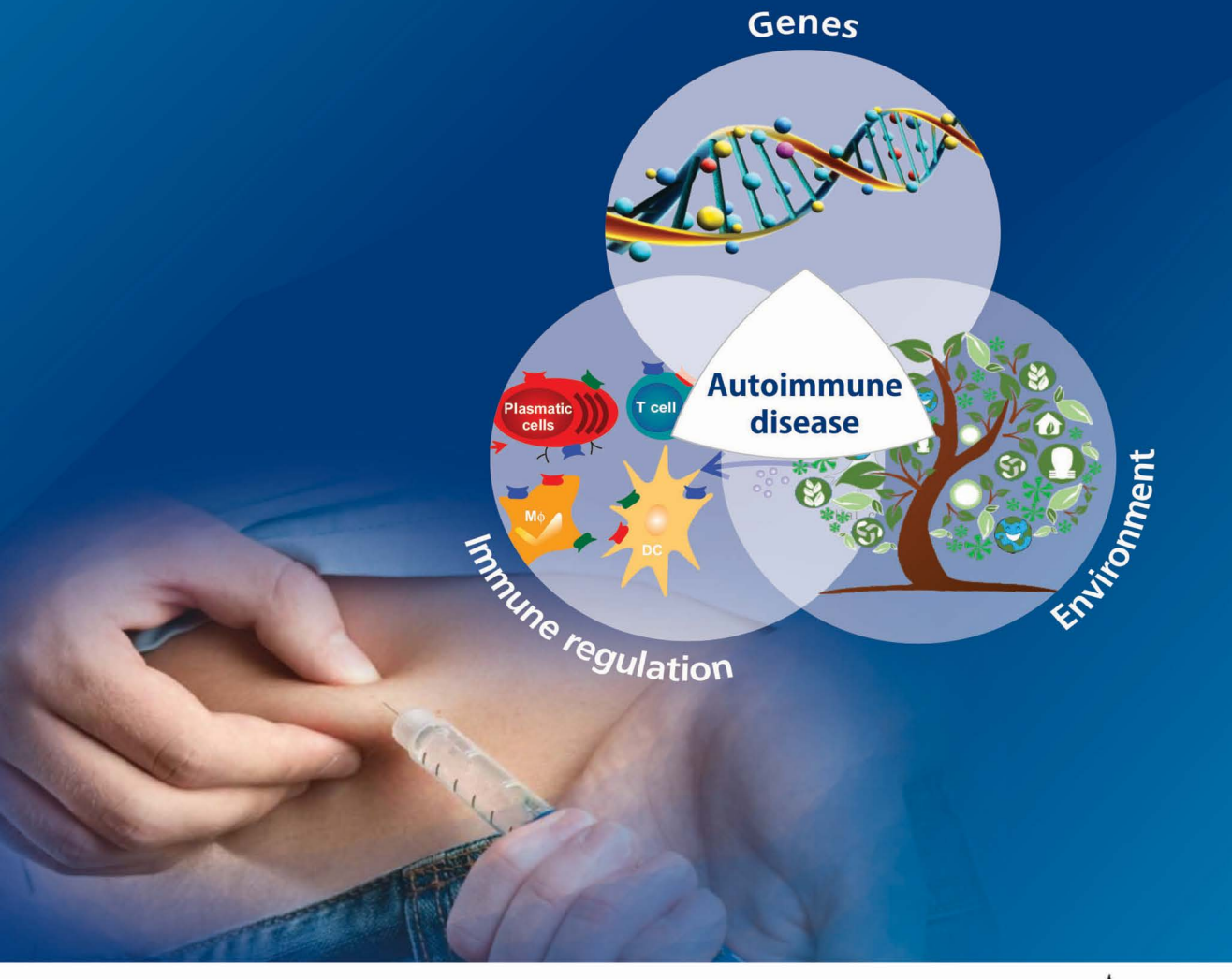

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CHAPTER 3

Monogenic Diabetes: Perspectives and Clinical Implications from Pediatric to Adult Endocrinology

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INTRODUCTION

Diabetes in childhood and adolescence currently comprises a wide range of different types of diabetes: (i) type 1 diabetes mellitus (T1DM), (ii) type 2 diabetes mellitus (T2DM), (iii) other specific types, (iv) gestational diabetes mellitus (GDM). The "other specific types" include the following:[1]

- Monogenic defects of β-cell function
- Mitochondrial diabetes
- Genetic defects in insulin action
- Drug- or chemical-induced
- Infections
- Diseases of the exocrine pancreas
- Endocrinopathies
- Uncommon forms of immune-mediated diabetes
- Other genetic syndromes sometimes associated with diabetes.

The most common forms of diabetes—T1DM and T2DM—are polygenic, meaning the risk of developing these forms of diabetes is related to multiple genes. Polygenic forms of diabetes often run in families. Environmental factors, like increase in body weight due to unhealthy eating habits, physical inactivity, and other wrong lifestyle practices, play an important role for the development of T2DM.

MONOGENIC DIABETES—DEFINITION

Monogenic diabetes results from one or more defects in a single gene. The disease may be inherited within families as a dominant, recessive, or non-Mendelian trait or may present as a spontaneous case due to a *de novo* mutation. Well over 40 different genetic subtypes of monogenic diabetes have been identified to date, each having a typical phenotype and a specific pattern of inheritance.[2,3]

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Monogenic forms of diabetes account for about 1–5% of all cases of diabetes in young people. It is very important to differentiate monogenic from polygenic forms of diabetes, as the treatment approaches may be different. Also, counseling can be rendered to the families on the consequences and nature of the disorder, the probability of transmitting it, and the options available in treatment. Genetic testing needs to be carried out to avoid misdiagnosing "monogenic"to "polygenic"form.

MONOGENIC DIABETES—GENE MUTATIONS (TABLE 1)

- Beta-cell dysfunction monogenic diabetes (most common):
  - Genes that regulate β-cell function/development (transcription factors)

TABLE 1: Monogenic diabetes: Classification and characteristics

Classification	Characteristics
Beta-cell dysfunction monogenic diabetes	
Group A: Neonatal diabetes diagnosed within 6–12 months of life	
Transient neonatal diabetes mellitus	Transient neonatal diabetes from imprinting anomalies on 6q24
Permanent neonatal diabetes mellitus	Neonatal diabetes due to mutations in the *KATP* channel genes
	Neonatal diabetes due to mutations in *INS* gene
	Wolcott-Rallison syndrome
	Neonatal diabetes due to *GCK* mutations
	Immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome
	Other causes of neonatal diabetes
Group B: Familial mild hyperglycemia or diabetes—autosomal dominant (MODY)	
	Mild fasting hyperglycemia due to glucokinase gene mutations (GCK-MODY, MODY2)
	Familial diabetes due to HNF1A-MODY (MODY3) and HNF4A-MODY (MODY1)
Group C: Genetic syndromes—diabetes with extrapancreatic features	
	Diabetes insipidus, diabetes mellitus, optic atrophy, and deafness syndrome (Wolfram syndrome)
	Renal cysts and diabetes syndrome (HNF1B-MODY or MODY5)
	Mitochondrial diabetes
	Diabetes secondary to monogenic diseases of the exocrine pancreas
Insulin resistance monogenic diabetes	
	Primary insulin signaling defects due to mutations in the insulin receptor gene
	Monogenic lipodystrophies
	Ciliopathy-related insulin resistance and diabetes

MODY, maturity-onset diabetes of the young; KATP, adenosine triphosphate-sensitive potassium.

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- Insulin resistance monogenic diabetes (rare):
  - Genes that regulate insulin action.

MONOGENIC DIABETES—DIAGNOSIS

The majority of patients with genetically proven monogenic diabetes are initially incorrectly diagnosed as T1DM or T2DM. The correct diagnosis is crucial: To predict the clinical course of the patient; to explain other associated clinical features; to guide the most appropriate treatment; and for clinical implications for other family members—often correcting the diagnosis and treatment. Thus, correct clinical and genetic diagnosis facilitates optimum diagnosis, genetic counseling, and therapy.

BETA-CELL DYSFUNCTION MONOGENIC DIABETES

It can be classified as:

- Group A: Neonatal diabetes (NDM)
  - Diagnosed within 6–12 months of life
- Group B: Familial mild hyperglycemia or diabetes
  - Autosomal dominant
- Group C: Genetic syndromes—diabetes
  - With extrapancreatic features.

Group A: Neonatal Diabetes—Diagnosed within 6–12 Months of Life

- Neonatal diabetes is insulin requiring diabetes which is usually diagnosed in the first 6–12 months of life
- Transient neonatal diabetes mellitus (TNDM)
  - That resolved at a median of 12 weeks and then did not require any treatment, although as many as 50% of cases would ultimately relapse
- Permanent neonatal diabetes mellitus (PNDM)
  - Required continual treatment from diagnosis.

Neonates who are diagnosed as having NDM usually have low birth weight compared to neonates of same gestational age. Insulin apart from its effects on glucose metabolism also contributes to growth promotion during fetal development, and hence, decrease in insulin during this period can be one of the causes of low weight compared to neonates of same gestational age. Two types of NDM exist: PNDM and TNDM. In PNDM category, these neonates will require lifelong treatment to control their blood glucose levels. In neonates whose diabetes remits within few weeks or months are classified as TNDM. Diabetes may relapse later in life in TNDM. Clinical features including type of presentation, associated features will guide during planning for genetic testing The details of the monogenic subtypes of neonatal and infancy onset diabetes are given in appendix table A1.

Transient Neonatal Diabetes Mellitus[4,5]

Characteristics of transient neonatal diabetes mellitus have been mentioned in table 2.

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TABLE 2: Characteristics of transient neonatal diabetes mellitus

Gene/inheritance	Age (weeks)/ diagnosis	Other features	Pancreas appearance
ZAC/HYAMI (imprinting defect on 6q24), 70%	0.5/ (0–4)	Macroglossia (23%)	Normal
Kir6.2 (KCNJ11), 25%	6/(0–260)	Developmental delay (20%) Epilepsy (6%) Diabetic ketoacidosis (30%)	Normal
SUR1 (ABCC8)	6/(0–17)	Developmental delay	Normal
HNF-1β dominant (60%), spontaneous	–	Renal developmental disorders	Atrophy

Permanent Neonatal Diabetes Mellitus[6-11]

Sulfonylurea receptor mutations

Sulfonylurea receptor mutations are given in table 3.
Phenotypes of sulfonylurea mutations:

- Transient neonatal diabetes mellitus
- Permanent neonatal diabetes mellitus
  - Developmental delay and neonatal diabetes [intermediate DEND (iDEND)]
  - Developmental delay, epilepsy, and neonatal diabetes (DEND).

Neonatal Diabetes Due To Mutations in the Adenosine Triphosphate-Sensitive Potassium Channel Genes

Sulfonylurea medications can be started (transfer from insulin as per an inpatient protocol), and are effective (improvement in glycemic control, without increasing hypoglycemia) in up to 90% of patients who have mutation in adenosine triphosphate-sensitive potassium (KATP) channel genes. Sulfonylurea (e.g., glibenclamide) dose requirement is usually high in this group, requiring about 0.5 mg/kg/day to even 2.3 mg/kg/day in few subjects; however, the dose requirement usually decreases over a period of time and these patients can maintain their target blood glucose range. Type 2 diabetes mellitus patients do not require such high doses of sulfonylurea. Also, per information from few brains imaging studies, it is observed that sulfonylurea may cross the blood brain barrier and improve neurological symptoms to some extent. Discoloration of teeth and diarrhea, though transient, are the side effects noted with this group of drugs.

TABLE 3: Sulfonylurea receptor mutations

Gene/inheritance	Age (weeks)/ diagnosis	Other features	Pancreas appearance
Kir6.2 (KCNJ11) (50%)	6/(0–260)	Developmental delay (20%) Epilepsy (6%) Diabetic ketoacidosis (30%)	Normal
SUR1 (ABCC8)	6/(0–17)	Developmental delay	Normal

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Other Mutations

Other mutations are given in table 4.

Neonatal Diabetes Due to Mutations in INS Gene[12,13]

Commonest cause of PNDM is KATP channel mutations. Next in line is mutation in the coding region of the *INS* gene (heterozygous). Beta-cell death occurs due to trapping and accumulation of misfolded proinsulin molecules in the endoplasmic reticulum (endoplasmic reticulum stress and β-cell apoptosis). Genetic *INS* mutations testing should be considered in other antibody negative "T1DM" infants/children, as sometimes *INS* gene mutation may cause diabetes onset after 6 months of age.

Wolcott-Rallison Syndrome[14]

Mutations—biallelic, in the gene encoding EIF2AK3 (eukaryotic translation initiation factor α-2-kinase 3) causes Wolcott-Rallison syndrome. This syndrome is a rare type of recessively inherited disease. This syndrome is characterized by early onset diabetes, spondyloepiphyseal dysplasia leading to growth retardation, and recurrent hepatic and/or renal dysfunction. In most of the cases, the onset of diabetes is seen in the first few months of life, however, it might present after 3–4 years of age also. Diagnosis of Wolcott-Rallison syndrome should be considered in children with PNDM and born of consanguineous marriage, and from a highly inbred population.

TABLE 4: Other mutations

Gene/inheritance	Age (weeks)/ diagnosis	Other features	Pancreas appearance
INS	9/(0–26)	None	Normal
EIF2AK3 Wolcott-Rallison syndrome/recessive	13 (6–65)	Epiphyseal dysplasia (90%), osteopenia (50%), acute liver failure (75%), developmental delay (80%), hypothyroidism (25%); insulin requiring	Atrophy of pancreas (?), exocrine dysfunction (25%)
FOXP3	6 (0–30)	Only boys affected	?
GCK (glucokinase)/ recessive (homozygous/ compound heterozygous)	–	Parents have fasting hyperglycemia as heterozygotes	Normal
IPF1/recessive	–	Parents may have early-onset diabetes as heterozygotes	Absent
PTF1A/recessive	–	Severe neurological dysfunction and cerebellar hypoplasia	Atrophy
IPEX syndrome/X linked (monogenic autoimmune diabetes)	–	Chronic diarrhea with villous atrophy (95%); pancreatic and thyroid autoantibodies (75%), thyroiditis (20%), eczema (50%); anemia (30%), often die young (first year)	–

IPEX, immunodysregulation polyendocrinopathy enteropathy X-linked syndrome

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Neonatal Diabetes Due to GCK Mutations[15]

The *GCK* mutations can also cause PNDM (2–3% of cases). This should be considered in children born to parents with mild fasting hyperglycemia. Parents do not display any symptoms of hyperglycemia, and hence, fasting blood glucose should be checked in parents of children having NDM, irrespective of consanguinity or family history of diabetes. Treatment with sulfonylurea has not produced any clear results in these children.

Immunodysregulation Polyendocrinopathy Enteropathy X-linked Syndrome[16]

Immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome is the only established form of "autoimmune" (β-cell autoimmunity and pancreatic islet autoantibodies) PNDM and occurs due to mutations in the *FOXP3* gene. This is X-linked and characterized by immune dysregulation, polyendocrinology, and enteropathy. The IPEX syndrome should be considered in young male infants presenting with diabetes, immune deficiency, severe infections, and diarrhea. Treatments include insulin for diabetes, and steroids and sirolimus for enteropthy. Allogeneic bone marrow transplant with reduced intensity conditioning can be considered. Gene therapy approaches are in the experimental stage.

Other Causes of Neonatal Diabetes

The clinical features in other causes of neonatal and infancy-onset diabetes have been described.[2,3] Fecal elastase and fecal fats are the best tests, functional, to assess the exocrine pancreas (pancreas imaging not reliable). Pancreatic supplements can be used if pancreatic hypoplasia/aplasia is detected. All causes of NDM, apart from KATP channel mutations, need insulin therapy.

Group B: Familial Mild Hyperglycemia or Diabetes—Autosomal Dominant (Maturity-onset Diabetes of the Young)[17]

Each genetic subtype of maturity-onset diabetes of the young (MODY) has its own pattern of hyperglycemia, age of onset, associated symptoms, hereditary or consanguinity component, and response to treatment, etc. Though MODY has a strong family history, first time genetic mutations (sporadic *de novo*) are also observed.

Common subtypes of MODY and additional clinical features are outlined in table 5. The clinical and molecular characteristics of "Maturity Onset Diabetes of Young" subtypes are given in appendix table A2.

Group C: Genetic Syndromes—Diabetes with Extrapancreatic Features[2,3]

A monogenic disorder should be considered in any child with diabetes associated with multisystem extrapancreatic features. These syndromes may either cause NDM or present in later life (Tables 5 and 6).

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TABLE 5: Common subtypes of maturity-onset diabetes of the young and additional clinical features

Gene/ inheritance	Age (years)/ diagnosis	Glucose at diagnosis (mmol/L)	Other features
HNF1α (MODY3)	14/(4–18)	17/(11–26)	• Large increment in an OGTT (2-h–0 h usually >5 mmol/L) • Low renal threshold • Progressive hyperglycemia with age • Sensitive to sulfonylureas
HNF4α (MODY1)	17/(5–18)	15/(9–20)	• Similar to *HNF-1α*, but renal threshold normal • Macrosomia very common and 20% have prolonged neonatal hypoglycemia • Sensitive to sulfonylureas
GCK (MODY2)	10/(0–18)	11/(5.5–16)	• Usually incidental finding at diagnosis • Fasting glucose in range 5.5–8 mmol/L • Small increment in an OGTT (2h–0 h usually <3.5 mmol/L) • Little deterioration in glycemia with age

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

- *HNF1α /HNF4α*-MODY: Sulfonylureas as first-line drug; insulin
- *GCK*-MODY, -MODY2: Most frequent form in pediatric patients; fasting hyperglycemia or mild diabetes; low birth weight. Diet only; insulin during pregnancy
- *GCK*-PNDM: *GCK* (glucokinase) recessive (homozygous/compound heterozygous), insulin + sulfonylureas; parents have fasting hyperglycemia as heterozygotes.

TABLE 6: Genetic syndromes—diabetes with extrapancreatic features

Gene/inheritance	Age (years)/ diagnosis	Treatment	Other features
WFS1; recessive (Wolfram syndrome)	<16	Insulin (nonautoimmune β-cell death)	DIDMOAD: Optic atrophy, diabetes insipidus, sensory neural deafness, dilated renal tracts, truncal ataxia, other neurological signs; death 30 years median age
HNF1β (MODY5)	–	Insulin requiring	Renal development disorders, renal cysts, renal dysplasia, uterine and genital anomalies, hyperuricemia, gout, abnormal liver function test. Pancreas atrophy, subclinical exocrine deficiency Not sensitive to sulfonylureas; insulin requiring
mtDNA: 3242 (A to G) $tRNA^{Leu(UUR)}$; mitochondrial diabetes: Maternal transmission	> Pediatric range	Insulin	Sensory neural deafness, short stature Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke (MELAS) syndrome
SLC19A2; recessive (Roger syndrome)	–	Insulin Thiamine ±	Thiamine responsive megaloblastic anemia, sensorineural deafness

MODY, maturity onset diabetes of the young; DIDMOAD, Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy and Deafness.

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TABLE 7: Monogenic diabetes—insulin resistance syndromes: Additional clinical features

Gene/inheritance	Age (years)/ diagnosis	Other features
Insulin receptor; leprechaunism (recessive)	Congenital	Abnormal facies, large genitalia; small for gestational age and growth retardation; rarely survive infancy
Insulin receptor; Rabson-Mendenhall (recessive)	Congenital	Extreme growth retardation, abnormal dentition
Insulin receptor; type A (recessive)	Adole scence	Insulin resistance in absence of obesity
Total: Seipin and *AGPAT2* (recessive) Partial: Lamin *AC* and *PPARG* (dominant); lipodystrophy	Congenital or adolescence	Loss of subcutaneous fat—partial or total

INSULIN RESISTANCE MONOGENIC DIABETES

Monogenic Diabetes—Insulin Resistance Syndromes[18]

These syndromes are summarized in table 7.

- Acanthosis nigricans
- Androgen excess
  - Hypertrichosis, polycystic ovarian syndrome
- Hyperinsulinemia—massive
  - In the absence of obesity
  - Hypertriglyceridemia
- Treatment (severe insulin resistance): very difficult
  - Metformin, thiazolidinediones ±: U 500 insulin—pumps
  - Recombinant leptin (total lipodystrophy).

In addition, insulin resistance syndrome subtypes, gene inheritance, leptin/adiponectin levels and associated clinical features are summarized in appendix table A3.

POPULATION PREVALENCE OF MONOGENIC DIABETES[19,20]

A challenging study has tried to evaluate dynamic changes in the prevalence of different types of diabetes in pediatric populations in Poland, with a specific focus on monogenic diabetes. The prevalence of monogenic diabetes in the pediatric population with a low prevalence of obesity remained stable and was nearly fivefold higher than that of T2DM and cystic fibrosis related diabetes (CFRD), justifying a need for increased access to genetic diagnostic procedures in diabetic children.

- Population of Polish children 0–18 years (December 2011)[19]
  - Prevalence of T1DM: 138/100,000
  - Prevalence of T2DM: 1.01/100,000
  - Prevalence of CFRD: 0.95/100,000
  - Prevalence of all monogenic diabetes: 4.6/100,000
  - Prevalence of PNDM: 1/300 000 = 0.3/100,000
  - Monogenic diabetes: 3.1–4.2% [5%] children with diabetes; 83% *GCK*-MODY

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- Population of United Kingdom Polish children 0–20 years: A large systematic study confirmed a prevalence of 2.5% of patients with monogenic diabetes who were less than 20 years of age in six United Kingdom clinics. This figure suggests that approximately 50% of the estimated 875 United Kingdom pediatric patients with monogenic diabetes have still not received a genetic diagnosis. This biomarker screening pathway is a practical approach that can be used to identify pediatric patients who are most appropriate for genetic testing.

MONOGENIC DIABETES: WHAT IT TEACHES US ON THE COMMON FORMS OF TYPE 1 AND TYPE 2 DIABETES MELLITUS?[21-23]

To date, more than 30 genes have been linked to monogenic diabetes. Candidate gene and genome-wide association studies have identified more than 50 susceptibility loci for common T1DM and approximately 100 susceptibility loci T2DM. About 1–5% of all cases of diabetes result from single gene mutations and are called monogenic diabetes. Pathophysiological basis of the role of monogenic diabetes genes that have also been found to be associated with common T1DM and/or T2DM are being elucidated.

GLUCOKINASE MONOGENIC DIABETES AND GESTATIONAL DIABETES MELLITUS[24]

Glucokinase monogenic diabetes (*GCK*-MODY) should be differentiated from "standard" GDM because management differs. In particular, intensive glycemic control, may adversely affect the fetus of a pregnant woman with *GCK*-MODY. In contrast to GDM, which is associated with a greatly increased risk for subsequent diabetes, women with *GCK*-MODY, and their affected offspring, have a low prevalence of diabetes complications and do not require treatment outside of pregnancy.

CONCLUSION

Monogenic forms of diabetes should be expected with the frequency of about 5% of all children/patients with diabetes. Diabetes with unusual course of the disease or other coexisting disorders in children or young adults may suggest monogenic diabetes. Some forms of monogenic diabetes may require specific method of treatment.

Many clinical subgroups and specific entities of monogenic diabetes are now known, due to identification of the gene causing the disease through advanced molecular genetic testing. This method of testing is nowadays used to confirm the specific disease type. However, since these tests are costly, in resource limited settings, they should be ordered only if these will be value addition to the strong suspicion of the clinician, based on the overall clinical presentation and profile. Genetically determined wide clinical heterogeneity and spectrum of "monogenic diabetes" are becoming increasingly apparent, extending across all ages of diabetes onset—from neonate and infancy, to childhood, adolescence and youth, and even adults. Accumulating new science in this field can lead to future practical implementation of "diabetes pharmacogenomics" and "personalized medicine".[2,3]

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- This book is focused towards diabetes care in children by integrating scientific developments with practical management
- This book provides clinical paradigms for diagnosis and management of pediatric diabetes and related conditions
- The book has been divided into sections and each section has been headed by different sub-editors
- The book begins with brief introductory section followed by section on investigations and clinical examination
- Diabetes in special populations like infants, neonates, and toddlers have been discussed in further chapters
- Written by leaders in the field of diabetes and pediatric diabetes with extensive practical knowledge of day-to-day management of children with diabetes mellitus
- A valuable addition to any library, useful, not only to pediatricians and diabetologists but also to postgraduate students.

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