Practical Endocrinology and Diabetes in Children

4th edition

Malcolm D. C. Donaldson, John W. Gregory, Guy Van Vliet, and Joseph I. Wolfsdorf

WILEY Blackwell

Practical Endocrinology and Diabetes in Children

Practical Endocrinology and Diabetes in Children

Fourth Edition

Malcolm D.C. Donaldson **MD, FRCP, FRCPCH, DCH**

Honorary Senior Research Fellow
Glasgow University School of Medicine
Honorary Consultant Paediatrician
Royal Hospital for Children
Glasgow, UK

John W. Gregory **MBChB, MD, FRCP, DCH, FRCPCH**

Professor in Paediatric Endocrinology & Honorary Consultant
Division of Population Medicine, School of Medicine
Cardiff University
Cardiff, Heath Park, Cardiff, UK

Guy Van Vliet **MD**

Staff Endocrinologist
CHU Sainte-Justine and Professor of Pediatrics
University of Montreal
Montreal, QC, Canada

Joseph I. Wolfsdorf **MB, BCh, MA, DCH, FCP, FAAP**

Attending Physician in Endocrinology
Boston Children's Hospital Chair in Endocrinology
Professor of Pediatrics, Harvard Medical School
Boston, Massachusetts, U.S.A.

Guest chapter "An Endocrinologist's Guide to Genetics in the Age of Genomics" contributed by

Johnny Deladoëy **MD, PhD**

Staff Endocrinologist
CHU Sainte-Justine and Associate Professor of Pediatrics
University of Montreal
Montreal, QC, Canada

WILEY Blackwell

Edition History: edition 1, 2001
edition 2, 2007
edition 3, 2011

Registered Office(s)
John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030, USA
John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

Editorial Office
9600 Garsington Road, Oxford, OX4 2DQ, UK

For details of our global editorial offices, customer services, and more information about Wiley products visit us at www.wiley.com.

Wiley also publishes its books in a variety of electronic formats and by print-on-demand. Some content that appears in standard print versions of this book may not be available in other formats.

Library of Congress Cataloging-in-Publication Data

Names: Donaldson, Malcolm D. C., author. | Gregory, John W., author. | Van Vliet, Guy, author. | Wolfsdorf, Joseph I., author. | Preceded by (work): Raine, Joseph E. Practical endocrinology and diabetes in children.
Title: Practical endocrinology and diabetes in children / Malcolm D.C. Donaldson, John W. Gregory, Guy Van-Vliet, Joseph I. Wolfsdorf ; guest chapter "Genomics for the pediatric endocrinologist" contributed by Johnny Deladoëy.
Description: Fourth edition. | Hoboken : Wiley-Blackwell, 2019. | Preceded by: Practical endocrinology and diabetes in children / Joseph E. Raine, Malcolm D.C. Donaldson, John W. Gregory, Guy Van Vliet. Third edition. Chichester, West Sussex, UK : Wiley-Blackwell, 2011. | Includes bibliographical references and index. |
Identifiers: LCCN 2018048129 (print) | LCCN 2018049204 (ebook) | ISBN 9781119386193 (Adobe PDF) | ISBN 9781119386025 (ePub) | ISBN 9781119386032 (hardcover)
Subjects: | MESH: Endocrine System Diseases | Diabetes Mellitus | Child
Classification: LCC RJ420.D5 (ebook) | LCC RJ420.D5 (print) | NLM WS 335 | DDC 618.92/462–dc23
LC record available at https://lccn.loc.gov/2018048129

Cover Design: Wiley
Cover Image: © asiseeit/iStock.com

Set in 9.25/11.5pt Minion by SPi Global, Pondicherry, India

10 9 8 7 6 5 4 3 2 1

Malcolm Donaldson, John Gregory, Guy Van Vliet and Joseph Wolfsdorf would like to dedicate this fourth edition to their long-suffering wives: Julia, Katrin, Chantal, and Gail, with love and thanks for their support.

Contents

Preface to the Fourth Edition

It was Dr Joseph Raine, Consultant Paediatrician at The Whittington Hospital in London, who recognized the gap between the large detailed endocrine reference books and short reviews of topics in paediatric endocrinology and diabetes. *Practical Endocrinology and Diabetes in Children* was Joe's brainchild, aiming to provide a practical, concise and up-to-date account of paediatric endocrinology and diabetes in a readable, user-friendly and portable format.

The first edition of the book featured an all-British cast of co-editors – Joe Raine, Malcolm Donaldson, John Gregory, and Martin Savage. Following its debut and favourable reception, the need to appeal to a wider readership was recognized, and Raymond Hintz (1939–2014) from Stanford University in California was invited to help with the second edition in 2007. For the third edition in 2011, Guy Van Vliet from Montreal in Canada joined the team to replace Martin Savage, further reinforcing the book's transatlantic credentials. Joe Raine has decided to stand down before this fourth edition and in his place Joseph Wolfsdorf from Harvard University has joined the team, taking on the diabetes and hypoglycaemia chapters.

Despite the addition of two North American editors, the book remains rooted in UK practice but with increasing North American and global emphasis. The accumulation of more data to impart, particularly in the field of diabetes, has resulted in a slightly longer book but it nevertheless retains the spirit of user-friendliness and conciseness of Joe Raine's original vision.

As with previous editions, space has been given to describe the practical management of diabetes in detail. The trend towards consensus guidelines over the past decade is reflected in this new edition and at the end of each chapter there are sections on when to contact a specialist centre, controversial areas, transition, potential pitfalls, and future developments.

At the end of the chapters there are also four to five interesting cases which illustrate diagnostic difficulties and management choices. These 'grey cases' are intended to be helpful for those studying for postgraduate examinations.

The book is aimed primarily at paediatricians in general hospitals and at junior paediatric staff with an interest in paediatric endocrinology and diabetes. Nurses working in paediatric endocrinology wards, diabetic nurse specialists, and medical students should also find it useful. Three of the four editors (MD, JG, GVV) have been on the teaching faculty of the European Society for Paediatric Endocrinology (ESPE) Winter School. This experience has made us conscious of the practical difficulties encountered by doctors in resource-limited countries and we hope that the text of our book reflects this awareness.

Finally, we are delighted to welcome Johnny Deladoëy from Montreal, Canada, who has contributed a guest chapter on genomics for the paediatric endocrinologist, in recognition of the importance of the area to modern practice, and the need for trainees and clinicians to have a basic working knowledge of molecular diagnosis.

MDCD, JWG, GVV, JIW
December 2018

Acknowledgements

The authors would like to thank Dr David Neumann, Faculty of Medicine in Hradec Kralove and University Hospital Hradec, Czech Republic, Ms Karen Smith, Department of Biochemistry, Glasgow Royal Infirmary, Dr Jane McNeilly, Department of Biochemistry, Royal Hospital for Children, Glasgow, Dr Robert Lindsay, British Heart Foundation Cardiovascular Research Centre, Glasgow, Dr Heather Maxwell, Department of Nephrology, Royal Hospital for Children, Glasgow, Dr Jarod Wong, Glasgow University School of Medicine, Dr Avril Mason, Royal Hospital for Children, Glasgow, Dr Esther Kinning, West of Scotland Department of Medical Genetics, Glasgow, Dr Judith Simpson, Neonatal Department, Queen Elizabeth Hospital, Glasgow, Dr Renuka Dias, Birmingham Children's Hospital, Professor Michael Preece, Institute of Child Health, London, Professor Tim Cole, UCL Institute of Child Health, London, Professor Peter Hindmarsh, University College London Hospitals and Great Ormond Street Hospital for Children, London, Professor Martin Savage, London Clinic Centre for Endocrinology, Queen Mary, University of London, Professor Juliane Léger, Hôpital Universitaire Robert Debré, Paris, Professor Marc Nicolino, Hôpital Mère-Enfant de Lyon, France, Dr Asmahane Ladjouze, CHU Bab El Oued, Algiers, Algeria, Dr Philippe Campeau Medical Genetics Service, Hôpital Sainte-Justine, Montréal, Canada, and Dr Nina Ma, Boston Children's Hospital, USA, for their help and advice with different sections of the book.

Abbreviations

ACEI	angiotensin converting enzyme inhibitor
ACMG	American College of Medical Genetics
ACR	albumin:creatinine ratio
ACTH	adrenocorticotrophic hormone
AER	albumin excretion rate
AFP	alpha-foetoprotein
AHO	Albright's hereditary osteodystrophy
AIRE	autoimmune regulator
AIS	androgen insensitivity syndrome
ALD	adrenoleukodystrophy
ALS	acid-labile subunit
ALT	alanine amino transferase
AME	apparent mineralocorticoid excess
AMH	anti-Müllerian hormone
APECED	autoimmune polyendocrinopathy with endocrinopathy and cutaneous ectodermal dystrophy
AR	androgen receptor
ARB	angiotensin receptor blocker
ARDS	adult respiratory distress syndrome
ATA	American Thyroid Association
ATD	anti-thyroid drug
ATP	adenosine triphosphate
AVP	arginine-vasopressin
β-hCG	β-human chorionic gonadotrophin
BDR	background diabetic retinopathy
BMI	body mass index
BOHB	beta-hydroxybutyrate
BP	blood pressure
CAH	congenital adrenal hyperplasia
CAI	central adrenal insufficiency
CAIS	complete androgen insensitivity syndrome
cAMP	cyclic adenosine monophosphate
CBG	cortisol binding globulin
CDC	Centers for Disease Control and Prevention
CDGA	constitutional delay in growth and adolescence
CF	cystic fibrosis
CFRD	cystic fibrosis-related diabetes
CGH	comparative genomic hybridization
CGM	continuous glucose monitoring
cGy	centi-Gray units
CNS	central nervous system
CPEG	Canadian Pediatric Endocrine Group
CPP	central precocious puberty
CRH	corticotrophin-releasing hormone
CRP	C-reactive protein
CSII	continuous subcutaneous insulin infusion
CT	computerized tomography
CVD	cardiovascular disease
CYP	cytochrome P450
DAX-1	dosage-sensitive sex reversal adrenal hypoplasia critical region on chromosome X, gene 1
DCCT	Diabetes Control and Complications Trial
DDAVP	desamino-D-arginine-vasopression
DEND	developmental delay, epilepsy, diabetes mellitus
DEXA	dual X-ray absorptiometry
DHEAS	dehydroepiandrosterone sulphate
dHPLC	denaturing high-performance liquid chromatography
DHT	dihydrotestosterone
DI	diabetes insipidus
DIDMOAD	diabetes insipidus, diabetes mellitus, optic atrophy, and deafness
DIT	diiodotyrosine
DKA	diabetic ketoacidosis
DMD	Duchenne muscular dystrophy
DME	diabetic macular oedema
DNA	deoxyribonucleic acid
DNE	diabetes nurse educator
DNS	diabetes nurse specialist
DOC	deoxycorticosterone
DSD	differences in sex development
DUOX2	dual oxidase 2 enzymes
DXA	dual X-ray absorptiometry
DZ	dizygotic
ECF	extracellular fluid
ENaC	epithelial sodium channel
EPP	ectopic posterior pituitary
ER	endoplasmic reticulum

ESPE	European Society for Paediatric Endocrinology
ESR	erthyrocyte sedimentation rate
FASD	foetal alcohol spectrum disorder
FBC	full blood count
FFA	free fatty acids
FGD	familial glucocorticoid deficiency
FGFR3	fibroblast growth factor receptor-3
FISH	fluorescent *in situ* hybridization
FNA	fine needle aspiration
FSH	follicle-stimulating hormone
FT3	free triiodothyronine
FT4	free thyroxine
GABA	gamma-aminobutyric acid
GAD	glutamic acid decarboxylase
GC	guanine-cytosine
GH	growth hormone
GHBP	growth hormone binding protein
GHD	growth hormone deficiency
GHRH	growth hormone releasing hormone
GI	glycaemic index
GNAS	G-protein stimulatory alpha subunit
GnRH	gonadotrophin-releasing hormone
GP	general practitioner
GSD 0	glycogen synthase deficiency
GSD 1	glucose-6-phosphatase deficiency
HbA1c	glycosylated haemoglobin
hCG	human chorionic gonadotrophin
HDL	high-density lipoprotein
hGH	human growth hormone
HGVS	Human Genome Variation Society
HHS	hyperglycaemic hyperosmolar state
HLA	human leukocyte antigen
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
H-P	hypothalamo-pituitary
HSD	hydroxysteroid dehydrogenase
IA2	insulinoma-associated antigen-2
	17-OHP 17-hydroxyprogesterone
1GF-1	insulin-like growth factor 1
im	intramuscular
IGFBP	insulin-like growth factor-binding protein
INS	insulin gene locus
IQ	intelligence quotient
ISCN	International System for Human Cytogenetic Nomenclature
ISPAD	International Society for Pediatric and Adolescent Diabetes
ISS	idiopathic short stature
ITT	insulin-tolerance test
IUGR	intrauterine growth restriction
IV	intravenous
JIA	juvenile idiopathic arthritis
K	potassium
LDL	low-density lipoprotein
LDLR	low-density lipoprotein receptor
LH	luteinizing hormone
MAF	minimum allele frequency
MASS	mitral valve prolapse, aortic enlargement, skin and skeletal
MC-1R	melanocortin-1 receptor
MDI	multiple daily injections
MEN	multiple endocrine neoplasia
MHC	major histocompatibility complex
MIT	monoiodotyrosine
MKRN3	Makorin ring finger protein 3
MODY	maturity onset diabetes of the young
MPH	mid-parental height
MR	mineralocorticoid receptor
MRAP	melanocortin 2 receptor accessory protein
MRI	magnetic resonance imaging
MTC	medullary thyroid carcinoma
MZ	monozygotic
NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
NC-21-OHD	non-classical 21-hydroxylase deficiency
NCHS	National Center for Health Statistics
NF	neurofibromatosis
NGS	next generation sequencing
NHS	National Health Service
NIS	sodium iodide symporter
NPH	neutral protamine Hagedorn
OGTT	oral glucose tolerance test
PAIS	partial androgen insensitivity syndrome
PALS	paediatric advanced life support
PCOS	polycystic ovarian syndrome
PCR	polymerase chain reaction
PDR	proliferative diabetic retinopathy
PG	plasma glucose
PGA	polyglandular autoimmune
PHA	pseudohypoaldosteronism
PHV	peak height velocity
PNDM	permanent neonatal diabetes mellitus
POMC	proopiomelanocortin
POR	P450-oxidoreductase
PPARγ	peroxisome proliferator-activated receptor gamma
PPGL	phaeochromocytoma and paraganglioma
PTH	parathyroid hormone
PTHrP	parathyroid hormone-related peptide
PTU	propylthiouracil
PUVA	psoralen plus ultraviolet A

PWS	Prader–Willi Syndrome
RCPCH	Royal College of Paediatrics and Child Health
RET	receptor tyrosine
RFLP	restriction length polymorphisms
RNA	ribonucleic acid
sc	subcutaneous
SDS	standard deviation score
SED	spondylo-epiphyseal dysplasia
SF-1	steroidogenic factor 1
SGA	small for gestational age
SHBG	sex hormone-binding globulin
SHOX	Short Stature Homeobox
SIADH	syndrome of inappropriate antidiuretic hormone secretion
SMBG	self-monitoring of blood glucose
SOD	septo-optic dysplasia
SRY	sex-determining region of the Y chromosome
StAR	steroidogenic acute regulatory (protein) T3 triiodothyronine
SV 21-OHD	simple virilizing 21-hydroxylase deficiency
SW 21-OHD	salt-wasting 21 hydroxylase deficiency
T3	triiodothyronine
T4	thyroxine
TBG	thyroid-binding globulin
TDD	total daily dose
td	three times a day
TFT	thyroid function tests
Tg	thyroglobulin
TH	transient hypothyroxinaemia
TNDM	transient neonatal diabetes mellitus
TPO	thyroid peroxidase
TRH	thyrotrophin-releasing hormone
TSH	thyroid-stimulating hormone
TSHR	thyroid-stimulating hormone receptor
TZD	thiazolidinedione
U&E	urea and electrolytes
UIC	urinary iodine concentration
UPD	uniparental disomy
VO_2	peak oxygen consumption
WBC	white blood cells
WES	whole exome sequencing
WHO	World Health Organization
ZnT8A	zinc transporter 8

1 Diabetes Mellitus

Definition

Diabetes mellitus is a heterogeneous disorder characterized by abnormal metabolism of carbohydrate, fat and protein with persistent fasting or postprandial hyperglycaemia resulting from defects in insulin secretion or insulin action (Skyler et al. 2017). It is diagnosed in one of four ways (see Table 1.1) (American Diabetes 2018). A fasting plasma glucose (PG) of 5.6–6.9 mmol/L (100–125 mg/dL) is considered prediabetes, whereas <5.6 mmol/L (<100 mg/dL) is normal. The oral glucose tolerance test (OGTT) is not recommended for routine clinical use. When classic symptoms are present, the diagnosis is usually straightforward and an OGTT is seldom needed; however, an OGTT may be indicated when mild hyperglycaemia is discovered without symptoms (e.g. in the sibling of a child with diabetes or in children with disorders such as cystic fibrosis (CF) that predispose to diabetes and may be asymptomatic in the early stages).

The incidental discovery of hyperglycaemia without classic symptoms does not necessarily indicate new onset diabetes, especially in young children with an acute illness, who may experience 'stress hyperglycaemia'. The risk of eventually developing diabetes may be increased in some children with incidental or stress hyperglycaemia, especially those with immunologic, metabolic, or genetic markers for type 1 diabetes, and consultation with a paediatric endocrinologist is indicated.

Diabetes mellitus is classified on the basis of its pathogenesis (Table 1.2); it may be the result of severe insulin deficiency or insulin resistance or, more commonly, a combination of milder defects in insulin secretion and action (American Diabetes Association 2018). This chapter primarily focuses on type 1 diabetes, which is the commonest form of diabetes in children. Other causes of diabetes are discussed in Sections 1.21 and 1.24.

Incidence

The incidence of type 1 diabetes in children varies considerably across the world with the Scandinavian countries having the highest incidence; in Finland, 60

Practical Endocrinology and Diabetes in Children, Fourth Edition. Malcolm D.C. Donaldson, John W. Gregory, Guy Van Vliet, and Joseph I. Wolfsdorf.

Table 1.1 Criteria for the diagnosis of diabetes mellitus.

1 Fasting plasma glucose ≥126 mg/dL (7 mmol/L)
or
2 Two-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test (OGTT)[b]
or
3 Haemoglobin A_{1c} ≥ 6.5% (48 mmol/mol)
or
4 In a patient with classic hyperglycaemia symptoms or hyperglycaemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

Definitions are based on venous plasma glucose levels. Glucose meters are useful for screening in clinics and physicians' offices, but the diagnosis of diabetes mellitus must be confirmed by measurement of venous plasma glucose on an analytic instrument in a clinical chemistry laboratory. In the absence of unequivocal hyperglycaemia, criteria 1 – 3 should be confirmed by repeat testing on a different day.
[a] Fasting is defined as no caloric intake for at least eight hours.
[b] OGTT should be performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.
[c] Haemoglobin A1c test should be performed in a laboratory using a method certified by the National Glycohemoglobin Standardization Program (www.ngsp.org).

Table 1.2 Protocol for and interpretation of the oral glucose tolerance test.

Indications
Confirmation of the diagnosis of diabetes mellitus in uncertain cases and diagnosis of impaired glucose tolerance

Preparation
Perform in the morning after fasting overnight for at least eight hours

Procedure
1 Pretest – plasma glucose sample
2 0 minute – administer oral glucose 1.75 g/kg (up to a maximum of 75 g) diluted with water (consume over 5–10 min.)
3 +2 hours – plasma glucose sample

Interpretation
1 Fasting plasma glucose >7.0 mmol/L (126 mg/dL) or 2 h concentration >11.1 mmol/L (200 mg/dL) are diagnostic of diabetes
2 2 h plasma glucose concentration >7.8 mmol/L (140 mg/dL) and <11.1 mmol/L (200 mg/dL) is impaired glucose tolerance
3 Fasting plasma glucose 6.1–6.9 mmol/L (100–125 mg/dL) is impaired fasting glucose

An OGTT should be performed after at least three days of adequate carbohydrate consumption (≥150 g per 1.73 m^2) and is performed using 1.75 g/kg anhydrous glucose dissolved in water for individuals ≤43 kg and 75 g for weight > 43 kg.

new cases per 100 000 children under 15 years of age. The United Kingdom, Canada, the US, and Australia also have high incidences with more than 20 cases per 100 000 children, whereas Asia and Sub-Saharan Africa have much lower rates (China and India 0.1 cases per 100 000 people each year) (Patterson et al. 2014). The reasons for these large variations are unclear but may include genetic factors given the evidence of variations in the incidence of diabetes in different ethnic groups (e.g. in the US, the incidence is higher in non-Hispanic white than African-American or Hispanic youth). However, this difference cannot solely be attributed to genetic factors. In Europe, the risk of type 1 diabetes differs substantially in people who are genetically close but separated by socioeconomic borders. Furthermore, over the past 30 years, the worldwide incidence has steadily increased across all age groups in parallel with an increased standard of living. A European population-based registry showed a 3.9% annual increase in the incidence of type 1 diabetes in children <15 years between 1989 and 2003 (5.4% in the 0–4 year age group) and the US population-based SEARCH for Diabetes in Youth study has shown that the prevalence in people <20 years increased by 21% between 2001 and 2009.

With some exceptions, type 1 diabetes incidence is related to geographic distance north of the equator, and the onset of disease appears to be higher in autumn and winter than in spring and summer. Table 1.3 presents the American Diabetes Association Classification of Diabetes.

Type 1 diabetes is a chronic autoimmune disease caused by an incompletely understood complex interaction between risk-conferring genes and environmental factors resulting over time (years) in immune-mediated, selective destruction and loss of function of pancreatic β-cell mass. This leads to insulin deficiency, symptoms from hyperglycaemia, and lifelong insulin dependence (Insel et al. 2015). Symptoms occur when approximately two-thirds of the pancreatic islets are devoid of ß-cells.

Table 1.3 The American Diabetes Association classification of diabetes.

Type 1 diabetes caused by autoimmune-mediated ß-cell destruction (and idiopathic forms of β-cell dysfunction) usually leading to severe or absolute insulin deficiency
Type 2 diabetes caused by progressive loss of insulin secretion on a background of insulin resistance.
Other specific causes of diabetes Monogenic diabetes syndromes such as neonatal diabetes and maturity-onset diabetes of the young (MODY) Diseases of the exocrine pancreas (such as cystic fibrosis) Drug- or chemical-induced diabetes such as with glucocorticoid use, drugs used for treatment of HIV/AIDS, or after organ transplantation
Gestational diabetes mellitus diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation

Although 90% of patients with type 1 diabetes do *not* have a family history of the disease, development of type 1 diabetes is strongly influenced by genetic factors. Children born into families with type 1 diabetes have different lifetime risks depending on whether the mother (6%), father (12%), or a sibling (5–10% by age 20 years) has the disease (Pociot and Lernmark 2016). If a twin develops type 1 diabetes, the lifetime risk for the non-affected dizygotic twin is 6–10%, whereas that for a monozygotic twin is approximately 60%.

Type 1 diabetes is a polygenic disorder; more than 50 susceptibility loci that contribute to the likelihood of developing type 1 diabetes have been identified. The major histocompatibility complex (MHC) region encoding the human leukocyte antigen (HLA) on chromosome 6p21 (the *IDDM1* locus) contributes about 50% of the genetic risk. The insulin gene locus (*INS*) is the second most important susceptibility locus, contributing about 10% of genetic susceptibility. Each of the loci identified through genome-wide association studies has a slight individual effect on the total genetic risk for progression to type 1 diabetes, and gene variants collectively explain ~80% of type 1 diabetes heritability (Pociot and Lernmark 2016).

Most of the loci associated with risk of type 1 diabetes are thought to involve immune responses (Concannon et al. 2009), supporting the notion that genetic influences involve mechanisms that collectively contribute to aberrant immune responsiveness. Genetic susceptibility might also influence responses to environmental stimuli, modify viral responses or physiological pathways. For most of the genetic loci, however, the molecular mechanism of action remains unknown.

Newborn screening has been used to identify children at increased genetic risk who have been followed for the appearance of autoantibodies against ß-cell autoantigens: insulin, glutamic acid decarboxylase (GAD), insulinoma-associated antigen-2 (IA2), and zinc transporter 8 (ZnT8A) that are known to be strongly associated with an increased risk for type 1 diabetes. These autoantibodies can appear as early as age six months, with a peak incidence in the second year of life in genetically susceptible individuals, i.e. they are present months to years before the onset of symptoms. Children who develop two or more islet autoantibodies have a markedly increased likelihood of eventually developing type 1 diabetes, and 100% of those who develop a third and, often, a fourth autoantibody develop clinical type 1 diabetes when followed for 20 years (Ziegler et al. 2013). At the time of diagnosis, more than 90% of individuals with type 1 diabetes have at least one autoantibody, and the presence of autoantibodies against ß-cell autoantigens is a key feature distinguishing type 1 from type 2 diabetes.

Type 1 diabetes is also associated with other autoimmune disorders, most commonly autoimmune thyroiditis. At the time of diagnosis, about 25% of children have thyroid autoantibodies, which predict thyroid dysfunction (most commonly hypothyroidism); Graves' disease occurs in ~0.5% of patients with type 1 diabetes. Addison's disease, likewise, occurs in approximately 0.5% of patients with type 1 diabetes. Coeliac disease is another immune-mediated disorder that occurs with increased frequency in patients with type 1 diabetes, and biopsy-confirmed coeliac disease occurs in 3.5% of individuals with type 1 diabetes compared with 0.3–1% in the general population.

Environment

The increase in incidence described above can only be explained by changes in environment or lifestyle and it is notable that migrants tend to acquire the same risk of type 1 diabetes as the native population in their new area of residence (Rewers and Ludvigsson 2016). Studies of prospective birth cohorts are attempting to identify potential triggers of islet autoimmunity and the natural history of progression to diabetes. Putative triggers include infections, diet, and toxins that affect children in utero, perinatally, or during early

childhood. See Rewers and Ludvigsson (2016) for a review of this topic.

Vaccines

There has been speculation that vaccines might trigger autoimmunity; however, no association has been detected with islet autoimmunity or type 1 diabetes, and a recent meta-analysis concluded that childhood vaccines do not increase the risk of type 1 diabetes (Morgan et al. 2016).

Idiopathic type 1 diabetes

Some forms of type 1 diabetes have no known aetiology. Most patients with idiopathic type 1 diabetes are of African or Asian ancestry. They have permanent insulinopenia and are prone to episodic ketoacidosis, but have no evidence of beta-cell autoimmunity (negative islet autoantibodies). This form of diabetes is strongly inherited but not HLA-associated. Between episodes, patients exhibit varying degrees of insulin deficiency and may intermittently need insulin replacement.

Biochemistry

Insulin is an anabolic hormone that acts on liver, fat, and skeletal muscle to increase glucose uptake, oxidation, and storage, and to decrease glucose production. Insulin also inhibits lipolysis and thereby limits the availability of fatty acids for oxidation and inhibits ketogenesis. Insulin is secreted in two major patterns – basal and in response to food (prandial). Basal secretion produces relatively constant, low plasma insulin levels that restrain lipolysis and hepatic glucose production (from glycogenolysis and gluconeogenesis). The blood glucose concentration is the dominant stimulus for insulin secretion. After a meal, in parallel with the rise in plasma glucose, circulating insulin concentrations rise rapidly, facilitating the entry of glucose into cells via glucose-specific transporters, particularly in skeletal muscle and adipose tissue. Insulin stimulates glycogen synthesis in the liver and skeletal muscle, inhibits hepatic gluconeogenesis, and stimulates fat storage and protein synthesis. Conversely, during fasting, plasma glucose concentrations and insulin secretion decrease, leading to reduced glucose uptake in muscle and adipose tissue, increased lipolysis, and stimulation of hepatic glucose production (from glycogenolysis and gluconeogenesis (Figure 1.1).

In type 1 diabetes, insulin deficiency results in hyperglycaemia and when the plasma glucose concentration exceeds the renal threshold for glucose reabsorption (~180 mg/dL or 10 mmol/L) osmotic diuresis occurs, causing polyuria and polydipsia. Insulin deficiency also causes increased lipolysis with the production of excess free fatty acids and ketoacids (beta-hydroxybutyrate (BOHB) and acetoacetate) leading to hyperketonaemia and ketonuria. When fluid losses exceed intake, particularly when nausea and vomiting occur (typical symptoms of ketosis), dehydration develops. The accumulation of ketoacids in the blood causes metabolic acidosis, which results in compensatory rapid, deep breathing (Kussmaul respiration). Acetone, formed from acetoacetate, accounts for the characteristic smell of the breath (described as the odour of nail polish remover or rotten fruit). Accompanying the lack of insulin is an increase in the levels of stress or counter-regulatory hormones (glucagon, catecholamines, cortisol, and growth hormone) whose metabolic actions are opposite to those of insulin. Thus, a lack of insulin together with increased concentrations of counter-regulatory hormones leads to progressive hyperglycaemia, hyperfattyacidemia, and ketosis and eventually ketoacidosis. Progressive dehydration, acidosis, and hyperosmolality cause decreased consciousness and lead to coma and death if untreated.

Clinical presentation

History

At diagnosis, typical symptoms have usually been present for only a few days to about two weeks or longer especially in type 2 diabetes:

- Polyuria (may cause secondary nocturnal enuresis)
- Polydipsia
- Weight loss
- Anorexia or hyperphagia
- Lethargy
- Constipation
- Infection (especially perineal candidiasis)
- Blurred vision
- Muscle cramps

Although most school-aged children report polyuria and polydipsia, these symptoms may be less obvious in the very young child (e.g. an infant in diapers) in whom the other less characteristic symptoms, especially perineal candidiasis, may predominate.

Clinical manifestations of diabetic ketoacidosis (DKA) include:

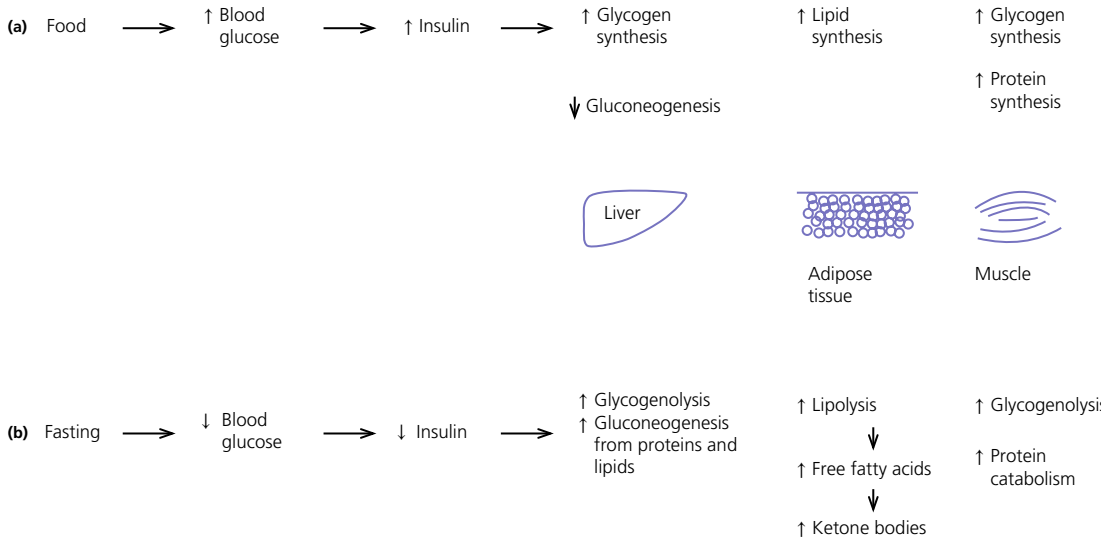

Figure 1.1 Glucose homeostasis: a comparison of (a) the fed state and (b) the fasting state.

- Dehydration
- Tachypnea; deep, sighing (Kussmaul) respiration
- Nausea, vomiting, and abdominal pain that may mimic an acute abdominal condition
- Drowsiness, confusion, progressive obtundation, and loss of consciousness.

Note that symptoms of systemic infection are infrequent; however, one must carefully look for an infection, especially if there is fever.

Examination

Patients with DKA typically are dehydrated. Clinical estimation of the degree of dehydration is imprecise and generally shows only fair to moderate agreement among examiners. The most useful signs for predicting 5% dehydration in young children are:

- prolonged capillary refill time (normal capillary refill is ≤1.5–2 seconds);
- abnormal skin turgor ('tenting' or inelastic skin).

Other useful signs to assess degree of dehydration include: dry mucous membranes, sunken eyes, absent tears, weak pulses, and cool extremities. More signs of dehydration tend to be associated with more severe dehydration; ≥10% dehydration is suggested by the presence of weak or impalpable peripheral pulses, hypotension, cool extremities, and oliguria.

Children diagnosed with diabetes should be immediately referred to a hospital for evaluation and management.

Differential diagnosis

The diagnosis of type 1 diabetes usually is obvious because the patient has classical symptoms (polyuria, polydipsia, and weight loss), random blood glucose is >11 mmol/L (200 mg/dL) and there is glucosuria with or without ketonuria. Diabetes should also be considered in the differential diagnosis of any child presenting with impaired consciousness and/or acidosis.

Tachypnea and hyperventilation in DKA may lead to the erroneous diagnosis of pneumonia or bronchiolitis. The lack of a cough or wheeze and the absence of abnormal findings on auscultation of the chest and a normal chest radiograph should raise the possibility of a metabolic acidosis such as DKA as the cause of tachypnea. Abdominal pain and tenderness in DKA may suggest a surgical emergency such as appendicitis or acute pancreatitis. Fluid, electrolytes, and insulin therapy will ameliorate the abdominal symptoms within hours. Diabetes should always be considered in children with secondary nocturnal enuresis and those with recurrent or persistent perineal candidiasis.

Acute illnesses such as severe sepsis or a prolonged convulsion may, occasionally, cause hyperglycaemia, glycosuria, and ketonuria. However, these biochemical abnormalities are almost always transient and are rarely associated with a history of previous polydipsia and polyuria. If in doubt, a fasting blood glucose measurement or OGTT (see Table 1.1) should be performed.

A doctor who either suspects or has made a definitive diagnosis of diabetes should immediately refer the child to a specialist for comprehensive assessment and initiation of treatment.

Investigations

At diagnosis, perform the following investigations:
- Plasma glucose concentration;
- Plasma BOHB concentration;
- Serum electrolytes, urea and creatinine concentrations (basic metabolic profile);
- Venous blood gas measurement;
- Complete blood count; note that leukocytosis and a raised C-reactive protein are common in DKA and do not necessarily indicate that an infection is present; an increased haematocrit reflects the degree of extracellular fluid (ECF) loss.
- A minority of children will have evidence of sepsis and need appropriate investigations (e.g. blood culture, chest radiograph, urine microscopy, and culture).
- HbA1c (glycated haemoglobin) is not necessary for initial management, but provides useful information about the duration and severity of antecedent hyperglycaemia.

The criteria for diagnosis of DKA are: plasma glucose ≥200 mg dL (11.1 mmol/L), venous pH < 7.30 or serum bicarbonate <15 mmol/L and 'moderate' or 'large' ketonuria, or serum BOHB ≥3 mmol/L (Wolfsdorf et al. 2018).

Initial management of newly diagnosed type 1 diabetes

Management of the child presenting without ketoacidosis

Hospitalization vs. Outpatient (home) treatment

The goals of initial management of the child with newly diagnosed diabetes mellitus are to restore the fluid and electrolyte balance, to stabilize the metabolic state with insulin, and to provide basic diabetes education and self-management training for the child (when age and developmentally appropriate) and caregivers (parents, grandparents, guardians, older siblings, day-care providers, and babysitters).

The diagnosis of diabetes in a child is a crisis for the family, who require considerable emotional support and time for adjustment and healing. Shocked, grieving, and overwhelmed parents require time to acquire basic ('survival') skills while they are coping with the emotional upheaval that typically follows the diagnosis of diabetes in a child. Even if they are not acutely ill, and depending on local resources and practices, children with newly diagnosed type 1 diabetes may be admitted to hospital to initiate insulin treatment and for diabetes education and self-management training. Outpatient or home-based management is preferred by some centres that have the requisite resources, in particular, the availability of travelling diabetes nurses who will need to visit at least daily in the first few days and maintain regular telephone contact, often outside normal working hours (Lowes and Gregory 2004). The size of the geographical area that needs to be covered is an important consideration. Outpatient or home-based management may have several advantages: the stress of a hospital stay is avoided, the outpatient setting or patient's home is a more natural learning environment for the child and family, and ambulatory treatment reduces the cost of care. Where adequate outpatient and/or home initial management of type 1 diabetes at diagnosis can be provided, studies have shown there is no disadvantage in terms of metabolic control nor increase in acute complications, hospitalizations, psychosocial or behavioural problems or total costs. The decision concerning whether a child with newly diagnosed diabetes should be admitted to hospital depends on several factors: most important are the severity of the child's metabolic derangements, the family's psychosocial circumstances, and the resources available at the treatment centre. Many paediatric diabetes centres offer ambulatory care and provide diabetes education and training in a day care unit for several days following diagnosis.

Hospital admission is necessary if intravenous (IV) therapy is required to correct dehydration, electrolyte imbalance, and ketoacidosis or if there are psychosocial challenges. Children who are ≤5% dehydrated, not nauseous or vomiting, who are not particularly unwell, and have a pH ≥7.30 usually respond well to subcutaneous insulin and oral rehydration.

Outpatient diabetes care

The diabetes team

Optimal care of children with type 1 diabetes is complex and time-consuming. Children with diabetes should be managed by a multidisciplinary diabetes team, which provides diabetes education and care in collaboration with the child's primary care physician. The team should consist of a paediatric endocrinologist or paediatrician with training in diabetes

management, a paediatric diabetes nurse educator (DNE) or diabetes nurse specialist (advanced practice nurse), a dietitian trained in paediatric diabetes nutrition, and a mental health professional (a clinical psychologist or medical social worker). The diabetes team should always be available by telephone to provide guidance and support to parents and patients and to respond to metabolic crises that require immediate intervention.

Initial diabetes education

Education is the foundation of diabetes care and is vital to ensure successful outcomes. Diabetes education provides the knowledge and skills needed to perform diabetes self-care and make the lifestyle changes required to successfully manage the disease. The diabetes education curriculum should be adapted to the individual child and family. Parents and children with newly diagnosed diabetes are usually anxious and overwhelmed and frequently cannot assimilate a large amount of abstract information. Therefore, the education programme should be staged. Initial educational goals should be limited to basic skills so that the child can be safely cared for at home and return to his or her daily routine as soon as possible. Initial diabetes education and self-management training should include: understanding what causes diabetes, how it is treated, how to measure and administer insulin, basic concepts of meal planning, self-monitoring of blood glucose (SMBG) and ketones, recognition, and treatment of hypoglycaemia, and how and when to contact a member of the diabetes team for advice.

Main topics for discussion following diagnosis

If several members of the diabetes team are involved in educating the newly diagnosed child and his or her family, good communication between team members to ensure consistency in the messaging and the specific information given is important. The following topics should be included in the curriculum and discussed with the child and family over a period of several weeks or months following diagnosis:

- Assessment of the family's pre-existing knowledge of diabetes.
- Current knowledge of the cause of diabetes.
- The consequences of having diabetes and its lifelong implications.
- The concept of the 'diabetes team' of professionals who will be involved in the child's care.
- The role of insulin in type 1 diabetes management.
- Practical details of insulin injections.
- When and how to monitor and interpret blood glucose concentrations.
- When and how to measure blood or urinary ketone concentrations.
- Advice about the crucial role of nutrition.
- The effect of exercise on carbohydrate and insulin requirements.
- The causes and consequences of hypoglycaemia and how to treat it.
- Management of diabetes during intercurrent illness ('sick days').
- The 'honeymoon period' of stable glycaemia and reduced insulin requirements following diagnosis.
- Long-term microvascular complications.
- Who to contact in an emergency (including phone numbers).
- Details of outpatient follow-up.
- The importance of always having identification (e.g. medical bracelet) indicating that the person has diabetes.
- Additional sources of information about diabetes.
- Availability of support groups.
- Health insurance issues, sources of and entitlement to financial assistance.
- Future developments.

Requirements on discharge from hospital

The child's primary care physician should be informed of the child's diagnosis, management plan, and discharge from hospital, and the diabetes nurse should communicate with the school nurse or daycare facility to ensure that details of the care plan are in place and understood. The equipment that a child will need on discharge is shown in Table 1.4.

Continuing diabetes education and long-term supervision of diabetes care

When the child is medically stable and parents (and other care providers) have mastered basic diabetes management skills, the child is discharged from the hospital or ambulatory treatment centre. In the first few weeks after diagnosis, frequent telephone contact provides emotional support and helps parents to interpret the results of blood glucose monitoring and, when necessary, insulin doses are adjusted to achieve blood glucose levels in a defined target range. Within a few weeks of diagnosis, many children enter a partial remission (the 'honeymoon' phase), evidenced by normal or near-normal blood glucose levels on a low

Table 1.4 Supplies required at time of discharge.

Lancing device and lancets
Blood glucose meter and test strips
Blood ketone meter and ketone strips or urine ketone test strips
Oral glucose tablets and gel
Glucagon emergency kit
Sharps container
Literature on diabetes management and how to obtain a Medic Alert bracelet/necklace
Pen insulin delivery system, disposable pre-filled pens, or syringes with needles for insulin injections
Insulin cartridges for non-disposable pen-delivery system or insulin vials
Rapid-acting and long- or intermediate-acting insulin (depending on insulin regimen)
Alcohol swabs
Needle clipper

dose (<0.25 U/kg/day) of insulin. By this time, most patients and parents are less anxious, have mastered basic diabetes management skills through repetition and experience, and are now more prepared to begin to learn the intricate details of intensive diabetes management. At this stage, the diabetes team should begin to provide patients and parents with the knowledge they will need to maintain optimal glycaemic control while coping with the effects of exercise, varying food intake, intercurrent illnesses, and the other challenges that normally occur in a child's daily life.

In addition to teaching facts and practical skills, education should promote desirable health beliefs and attitudes in the young person with a chronic incurable disease. For some children, this may be best accomplished in a non-traditional educational setting, such as a summer camp for children with diabetes. The educational curriculum must be concordant with the child's level of cognitive development and has to be adapted to the learning style and literacy and numeracy skills of the individual child and family. Parents, grandparents, older siblings, the school nurse, and other important people in the child's life are encouraged to participate in the diabetes education programme so they can actively share in the diabetes care and ensure that the child with diabetes is not excluded from normal childhood activities (sports, field trips, sleepovers, etc.).

In the first month after diagnosis, the patient and care providers are seen frequently by the diabetes team to review and consolidate the diabetes education and practical skills learned in the first few days and to extend the scope of diabetes self-management training. Thereafter, follow-up visits with members of the diabetes team should occur at least every three months. Regular clinic visits are necessary to ensure that the child's diabetes is being appropriately managed and the goals of therapy are being met. A focused history should obtain information about self-care behaviours, the child's daily routines, the frequency, severity, and circumstances surrounding hypoglycaemic events, details about insulin doses, and blood glucose monitoring data should be reviewed to identify patterns and trends. At each visit, height and weight are measured and plotted on a growth chart. The weight curve is especially helpful in assessing the adequacy of therapy. Significant weight loss usually indicates that the prescribed insulin dose is insufficient or the patient is not receiving all the prescribed doses of insulin. A complete physical examination should be performed at least once or twice each year focusing on blood pressure, stage of puberty, evidence of thyroid disease, examination of the injection sites for evidence of lipohypertrophy (from over-use of the site) or lipoatrophy, and mobility of the joints of the hands.

Each clinic visit provides an opportunity to reinforce the individual patient's blood glucose targets and HbA1c goal, and to increase the patient's and the family's understanding of diabetes management, the interplay of insulin, food, and exercise, and their impact on blood glucose levels. As the child's cognitive development progresses, the child should become more involved in diabetes management and increasingly assume *supervised* age-appropriate responsibility for daily self-care. Parents are encouraged to contact the diabetes team for advice if the pattern of blood glucose levels changes between routine visits, suggesting the need to adjust insulin doses or change the regimen. Eventually, when parents and patients have sufficient knowledge and experience to interpret blood glucose patterns and trends, they are encouraged to independently adjust insulin doses.

Psychosocial aspects of diabetes management

The diagnosis of diabetes in a child or adolescent hurls parents into a frightening and foreign world. They grieve the loss of their healthy child and have to cope with normal distress reactions, including shock,

disbelief and denial, fear, anxiety, anger, and blame or guilt. During this emotionally intense time, parents are expected to rapidly acquire an understanding of the disease and manage the illness at home. Parents should receive the necessary support to begin coping with their emotional distress and not be overwhelmed by unrealistic expectations from a well-meaning diabetes treatment team.

Diabetes also presents family members with the task of being sensitive to the balance between the child's need for a sense of autonomy and mastery of self-care activities and the need for ongoing family support and involvement. The struggle to balance independence and dependence in relationships between the child and family members presents a long-term challenge and raises different issues for families at different stages of child and adolescent development. Focusing on normal developmental tasks at each stage of the child's growth and development provides the most effective structure to address this concern (Anderson et al. 2009).

A medical social worker or clinical psychologist should perform an initial psychosocial assessment of all newly diagnosed patients to identify families at high risk who need additional services. Thereafter, patients are referred to a mental health specialist when emotional, social, environmental, or financial concerns are suspected or identified that interfere with the ability to maintain acceptable diabetes control. Some of the more common problems in families who have a child with diabetes include parental guilt, resulting in poor adherence to the treatment regimen, difficulty coping with the child's frustration and rebellion against treatment, fear of hypoglycaemia, anxiety, depression, missed appointments, financial hardship, or loss of health insurance affecting the ability to attend scheduled clinic appointments and/or purchase supplies. Patients with poor glycaemic control and a history of frequent emergency department visits should be screened for depressed mood (Lawrence et al. 2006). Recurrent ketoacidosis is the most extreme indicator of psychosocial stress, and management of such patients must include a comprehensive psychosocial assessment.

Because childhood is characterized by cognitive and emotional immaturity, successful treatment of paediatric diabetes requires the continuous, active involvement of responsible adults. Moreover, diabetes treatment occurs within a family dynamic, and treatment-related conflicts are common, arising in part from a natural discord in goals between caretakers and the child. Each phase of childhood has unique characteristics that complicate treatment; for example, the normally erratic eating behaviour of toddlers and the unscheduled intense physical play of school-aged children that can hinge on unpredictable factors, such as the weather. Adolescence is characterized by multiple physiologic and psychosocial factors that make glycaemic control even more challenging. Diabetes treatment should be individually tailored to each child, based on age, family resources, cognitive ability, the schedule and activities of the child and family, and their goals and desires.

Rates of psychological ill health in youth with diabetes are high, and longitudinal data indicate that mental health issues in childhood are likely to persist into early adulthood and are prognostic of maladaptive lifestyle practices, long-term problems with diabetes control and earlier-than-expected onset of complications. For these reasons, mental health screening should be routinely performed in diabetes clinics. Screening for behavioural disturbance should begin in children at the time of diagnosis, with further assessment of parental mental health and family functioning for those children identified to be 'at risk'. Interventions can then be targeted based on the specific needs of individual children and families. Additional psychological support is often provided by diabetes nurses and other parents at local and national support groups.

Diabetes Control and Complications Trial (DCCT)

This clinical trial, completed in 1993, proved that near-normal glycaemia delays the onset and slows the progression of microvascular complications, and it set the current standards for treatment of type 1 diabetes. A total of 1441 subjects with diabetes aged 13–39 years were randomized either: (i) to continue with their conventional treatment; or (ii) to receive intensive therapy with increased support from the 'diabetes team' and insulin administered either by three or more injections daily or by a pump (The Diabetes Control and Complications Trial Research Group 1993). After a mean duration of 6.5 years, as compared with conventional therapy, intensive treatment resulted in a reduction in:

- mean HbA1c concentration of nearly 2% (22 mmol/mol);
- the risk of retinopathy by 76%;
- the occurrence of microalbuminuria by 39%;
- the occurrence of neuropathy by 60%.

For every 10% reduction in HbA1c (e.g. 8% vs. 7.2%), there was a 44% reduction in the risk of microvascular complications.

Intensive treatment using the insulin preparations available at the time (i.e. before the development of insulin analogues) was associated with a two-to-three-fold increase in severe hypoglycaemia and a mean weight gain of 4.6 kg when compared with conventional treatment. This study clearly demonstrated that near-normal glycaemia (as measured by HbA1c) significantly reduced the risk of microvascular complications. In the 25 years since the results of this landmark study were announced, the challenge for clinicians has been to implement the principles of intensive diabetes therapy in children and adolescents in routine clinical practice.

Goals of therapy

The International Society for Pediatric and Adolescent Diabetes (ISPAD) recommends a target HbA1c of <7.5% (58 mmol/mol) for all age groups (DiMeglio et al. 2018). However, biochemical goals should be individualized, taking into account both medical and psychosocial considerations; i.e. each child should have individually determined targets with the goal of achieving an HbA1c value as close to normal as possible while avoiding frequent episodes of mild to moderate hypoglycaemia and severe hypoglycaemia. Less stringent treatment goals may be appropriate or more realistic for preschool-aged children, children with developmental handicaps, psychosocial challenges, lack of appropriate family support, children who have experienced severe hypoglycaemia, or those with hypoglycaemia unawareness.

Insulin therapy in type 1 diabetes

Initial insulin therapy

At the time of diagnosis, many children with type 1 diabetes are severely insulin-deficient and require insulin replacement to survive. The aim of insulin replacement therapy is to simulate normal plasma insulin patterns as closely as possible. Truly physiologic insulin replacement continues to be an elusive goal owing to: (i) delivery of insulin into the systemic circulation instead of the portal venous system, and (ii) the inability to mimic the first and second phases of normal insulin release in response to eating. Insulin pump therapy or multiple daily insulin (MDI) injections currently are the two methods that most closely mimic normal insulin secretion.

The *ideal* regimen for the newly diagnosed patient is a multiple dose, flexible basal-bolus regimen that provides basal insulin throughout the day and night and insulin boluses before meals and snacks. Rapid-acting insulin is injected approximately 15 minutes before eating; individual doses are adjusted meal-to-meal based on preprandial blood glucose values, anticipated meal macronutrient content, and physical activity. Practical considerations are vitally important when selecting an insulin regimen for a child with type 1 diabetes. Socio-economic circumstances, parental health literacy and numeracy, patient's age, supervision of care, ability and willingness to self-administer insulin several times each day, and difficulty maintaining long-term adherence, all conspire to make physiologic insulin replacement challenging. For these reasons, there is no universal insulin regimen that can be successfully used for *all* children with type 1 diabetes. The diabetes team must design an insulin regimen that meets the needs of the individual patient and is acceptable to the patient and family members(s) responsible for administering insulin to the child or supervising its administration.

The route of insulin administration initially is determined by the severity of the child's condition at presentation. Insulin is usually given intravenously for treatment of DKA; whereas insulin may be administered subcutaneously when children are metabolically stable without vomiting or significant dehydration and ketosis. Whenever appropriate, the newly diagnosed child should commence insulin replacement therapy with a flexible basal-bolus regimen. In some healthcare systems, it is now possible to start insulin pump therapy at the time of diagnosis regardless of the severity of presentation or age of the child.

Three major categories of insulin preparations, classified according to their time course of action, are available (Table 1.5) and various insulin replacement regimens consisting of a mixture of short- or rapid-acting insulin and intermediate- or long-acting insulin are used in children and adolescents, typically given at least two to four (or more) times daily.

Insulin analogues

Rapid-acting insulin analogues incorporate amino acid substitutions, which make them quickly dissociate into monomers following injection and are then rapidly absorbed. Compared with short-acting regular insulin, they produce lower postprandial glucose excursions.

Table 1.5 Types of insulin preparations and approximate insulin action profiles.

Insulin type	Onset of action (h)	Peak of action (h)	Effective duration of action (h)
Rapid-acting analogues			
Aspart, lispro, glulisine	0.25–0.5	1–3	3–5
Regular insulin	0.5–1	2–4	5–8
Intermediate-acting insulin			
Neutral Protamine Hagedorn (NPH), isophane	2–4	4–10	10–16
Long-acting analogues			
Detemir	2–4	None	12–20[a]
Glargine	2–4	None	20–24
Degludec	2–4	None	24–42
Premixed combinations			
50% NPH, 50% regular	0.5–1	dual	10–16
50% NPL, 50% lispro	0.25	dual	10–16
70% NPH, 30% regular	0.5–1	dual	10–16
70% PA, 30% aspart	0.25	dual	15–18
75% NPL, 25% lispro	0.25	dual	10–16

PA, protamine-crystallized insulin aspart suspension; NPL, neutral protamine lispro suspension. PA + soluble aspart and NPL + lispro are both stable pre-mixed combinations of intermediate- and rapid-acting insulins.
The human insulins and insulin analogues are available in vials, pre-filled disposable pen injectors, and cartridges for non-disposable pen injectors.
These data are approximations from studies in adult test subjects. The times of onset, peak, and effective duration of action vary within and between patients and are affected by numerous factors, including size of dose, site and depth of injection, dilution, exercise, temperature, regional blood flow, local tissue reactions.
[a] Dose-dependent; 12 hours for 0.2 U/kg; 20–24 hours for ≥0.4 U/kg.

The three long-acting insulin analogues are characterized by a relatively consistent and prolonged release of insulin without distinct peaks. Insulin glargine has a prolonged duration of action (22–24 hours) and can be injected at any time of day, but is usually given with dinner or at bedtime. The duration of action of insulin detemir is partly dependent on the dose – small doses may last only 12 hours; therefore, it usually has to be injected twice daily. Insulin degludec is an ultra-long-acting insulin with a flat, stable profile at steady state and a duration of action exceeding 24 hours and up to 42 hours. There is some evidence that both glargine and detemir lead to a decrease in the incidence of hypoglycaemia including nocturnal hypoglycaemia. Table 1.6 shows suggested starting total daily insulin dose (units per kg per day).

Table 1.6 Suggested starting total daily insulin dose (units per kg per day).

	No DKA at presentation	DKA at presentation
<6 years or HbA1c <7%	0.15–0.25	0.5–0.75
Prepuberty	0.25–0.5	0.75–1
Puberty	0.5–0.75	1–1.2
Postpuberty	0.25–0.5	0.75–1

While clinical trials comparable to the Diabetes Control and Complications Trial (DCCT) have not been conducted in prepubertal children, it is logical to extrapolate that prepubertal children will also benefit from near-normal glycaemic control. Intensive treatment regimens (MDI injections or insulin pump) are the preferred form of therapy for all patients with type 1 diabetes. Insulin regimens based on one or two daily injections cannot achieve optimal glycaemic control in type 1 diabetes except during the remission ('honeymoon') period, and may incur a greater risk of hypoglycaemia. These regimens, including the use of pre-mixed combination insulins, should only be used when insurmountable barriers preclude the use of a multiple dose insulin regimen.

Split-mixed insulin regimens

When a *two-dose regimen* is used, the total daily dose (TDD) is typically divided as follows: two-thirds before breakfast and one-third is given in the evening. The relative proportion of rapid- or short-acting insulin to intermediate-acting insulin depends on the pre-meal blood glucose value and the carbohydrate content of meals. It is common to start by giving one-third of the pre-breakfast dose as rapid- or short-acting insulin and two-thirds as neutral protamine Hagedorn (NPH), and a similar ratio before dinner. For example, if the TDD for a 30-kg child is 0.75 unit kg (22.5 units): a mixed dose injected before breakfast would consist of 5 units of rapid-acting and 10 units NPH; the pre-dinner dose would be 2.5 units rapid-acting and 5 units NPH. Regular insulin should be injected at least 30 minutes before eating; rapid-acting insulin (lispro, aspart, glulisine) is given 15 minutes before eating.

The optimal ratio of rapid- or short-acting to intermediate- or long-acting insulin for each patient is determined empirically, guided by the results of frequent blood glucose monitoring. At least five daily blood glucose measurements are required to determine the effects of each component of the insulin regimen: before each meal, before the bedtime snack, and once overnight between midnight and 4 a.m. Parents are taught to look for patterns of hyperglycaemia or hypoglycaemia that indicate the need for a dose adjustment. Adjustments are made to individual components of the insulin regimen, usually in 5–10% increments or decrements, in response to patterns of consistently elevated (above the defined target range for several consecutive days) or unexplained low blood glucose levels, respectively. The insulin dose is adjusted until satisfactory blood glucose control is achieved, i.e. at least 50% of blood glucose values are in or close to the child's target range.

At the time of diagnosis, most children have some residual beta-cell function and within several days to a few weeks often enter a period of partial remission ('the honeymoon period'), during which normal or nearly normal glycaemia is achieved with a low dose of insulin. At this stage, the dose of insulin must be reduced to prevent hypoglycaemia, but should not be discontinued. As destruction of the remaining beta-cells occurs over time, the insulin requirement increases ('the intensification phase'), eventually reaching a full replacement dose. The average daily insulin dose in prepubertal children with long-standing diabetes is approximately 0.6–0.8 units/kg/day, and in adolescents 1–1.2 units/kg/day. Obese patients usually are insulin-resistant and require relatively higher TDDs, e.g. overweight or obese adolescents may require up to 1.5 units/kg/day.

Beyond the remission period it is seldom possible without a regimented lifestyle and rigid adherence to a meal plan to achieve near-normal glycaemia with two injections per day and without incurring a greater risk of hypoglycaemia, especially overnight. An important limitation of a two dose 'split-mixed' regimen is that the peak effect of the pre-dinner intermediate-acting insulin (isophane, NPH) tends to occur at the time of lowest insulin requirement (i.e. from midnight to 4 a.m.), increasing the risk of nocturnal hypoglycaemia (Figure 1.2). Thereafter, insulin action decreases from 4 a.m. to 8 a.m., when basal insulin requirements normally increase. Consequently, the tendency for blood glucose levels to rise before breakfast ('the dawn phenomenon') is compounded by the waning insulin effect before breakfast and/or by counter-regulatory hormones secreted in response to a fall in blood glucose levels during sleep, resulting in post-hypoglycaemic hyperglycaemia (the Somogyi phenomenon, see Section 1.7.7.2).

A *three-dose insulin regimen* with mixed short- or rapid- and intermediate-acting insulin before breakfast, only short- or rapid-acting insulin before dinner, and intermediate- or long-acting acting insulin at bedtime, may ameliorate these problems (Figure 1.2). The peak action of the morning dose of NPH occurring at midday may eliminate the need for a dose of rapid-acting insulin at lunchtime (provided lunch does not contain excessive carbohydrate), and this may be necessary in circumstances where nobody is available to administer a pre-lunch dose of rapid-acting insulin to a young child. Insulin regimens that employ intermediate-acting insulin demand consistency in the daily dietary regimen, both with respect to the amounts and timing of food consumed at each meal and snack, and the timing of insulin injections. Furthermore, owing to the time and duration of its peak action, NPH insulin given at bedtime is associated with increased frequency of nocturnal hypoglycaemia as compared to long-acting, 'peakless' basal insulin analogues.

Basal-bolus regimens and continuous subcutaneous insulin infusion (CSII)

Flexible basal-bolus insulin regimens utilize MDI (Figure 1.3) or continuous subcutaneous insulin infusion (CSII) with an insulin pump (Figure 1.3). Flexible regimens more closely simulate normal diurnal insulin profiles, overcome many of the