Thieme

Diagnosis, Therapy and Follow-Up of Diabetes Mellitus in Children and Adolescents

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ABBREVIATIONS

µg	microgram
ABCC8 gene	gene localization for the sulfonylurea receptor 1
ACE	angiotensin-converting enzyme
ACR	albumin creatinine ratio
ADA	American Diabetes Association
ADHD	attention deficit/hyperactivity disorder
AER	albumin excretion rate
AGA	Working Group for Obesity/Arbeitsgemeinschaft für Adipositas
AGPD	Working Group for Paediatric Diabetology/Arbeitsgemeinschaft für Pädiatrische Diabetologie
AHCPR	Agency for Health Care Policy and Research
AIHA	autoimmune hemolytic anemia
Abs	antibodies
ALT	alanine transaminase = liver enzyme
APS	Working Group for Paediatric Metabolic Disorders/Arbeitsgemeinschaft für Pädiatrische Stoffwechselstörungen
APS	autoimmune polyglandular syndrome
AT_1 blocker	angiotensin II type 1 receptor blocker
AWMF	German Association of the Scientific Medical Professional Societies/Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BABYDIAB	German BabyDiab-Study (German baby diabetes study)
BAR	Federal Working Group for Rehabilitation/Bundesarbeitsgemeinschaft für Rehabilitation
BdKJ	Association of Diabetic Children and Adolescents/Bund diabetischer Kinder und Jugendlicher
BG	blood glucose
BMI	body mass index
BMI-SDS	body mass index standard deviation score
BS	blood sugar
CFRD	cystic fibrosis-related diabetes
CGM	continuous glucose monitoring
CK	creatine kinase
C-peptide	connecting peptide = part of proinsulin
CSII	continuous subcutaneous insulin injection = insulin pump
CT	computed tomography
DAG	German Obesity Society/Deutsche Adipositas Gesellschaft
DAISY	Diabetes Autoimmunity Study of the Young (autoimmunity study for adolescents with diabetes)
DCC-Trial	Diabetes Control and Complications Trial (study on the control and complications of diabetes)
DDG	German Diabetes Society/Deutsche Diabetes Gesellschaft
DENIS	German Nicotinamide Intervention Study/Deutsche Nicotinamide-Intervention-Study
DEPS-R	Diabetes Eating Problem Survey – Revised
DGE	German Nutrition Society/Deutsche Gesellschaft für Ernährung
DGEM	German Society for Nutritional Medicine/Deutsche Gesellschaft für Ernährungsmedizin
DGKJP	German Society for Paediatric and Adolescent Psychiatry, Psychosomatics and Psychotherapy/Deutsche Gesellschaft für Kinder- und Jugendpsychiatrie, Psychosomatik und Psychotherapie
diab.	diabetic
diabetesDE	Diabetes Germany
DIAMYD	Diamyd® Study
DIPP	Diabetes Prediction and Prevention Project
DKA	diabetic ketoacidosis
dl	decilitre
DNSG	Diabetes And Nutrition Study Group
DPT-1	Diabetes Prevention Trial – Type 1
DPM	Diabetes patient management (documentation system)
EASD	European Association for the Study of Diabetes
EDIC-Trial	Epidemiology of Diabetes Interventions and Complications Trial = Follow-up Study of the DCC Trial
EIF2AK3	gene locus for mutations leading to a genetic syndrome with diabetes
EC	evidence class (methodological quality of a study according to criteria of evidencebased medicine)
ECG	electrocardiogram
EMA	European Medicines Agency
ENDIT	European Nicotinamide Intervention Trial
ES	educational support (therapeutic support in parenting)
ethn.	ethnic
fam.	familiar
FES	family environment scale = scale for the evaluation of social characteristics and the environment of families
FOXP3	gene locus for mutations leading to genetic syndromes with diabetes
FST-D	family system therapy for patients with diabetes
fT3	free triiodothyronine
fT4	free thyroxine
g	gram
GAD	glutamate decarboxylase
GCK	glucokinase
h	hour
HbA1c	glycated haemoglobin
HDL	high-density lipoprotein
HHS	hyperosmolar hyperglycaemic syndrome

HLA	human leukocyte antigen
HNF	hepatocyte nuclear factor
HTA	health technology assessment = systematic assessment of medical technologies, procedures aids and organizational structures, in which medical services are provided
I.U.	international unit(s)
i. m.	intramuscular
IV	intravenously
IA-2	tyrosine phosphatase IA-2 antibody
IAA	insulin autoantibody
ICA	islet cell antibody
ICT	intensified conventional insulin therapy
IgA	immunoglobulin A
IgG	immunoglobulin G
INS	insulin(s)
IPEX	immunodysregulation polyendocrinopathy enteropathy X-linked syndrome
IPF-1	insulin promoter factor 1 = gene locus with mutations leading to MODY-4 diabetes
IRMA	intraretinal microvascular anomaly
ISPAD	International Society for Paediatric and Adolescent Diabetes
ITP	immune thrombocytopenic purpura
Y	years
n/a	not available
kcal	kilocalories
KCNJ11	inward-rectifier potassium ion channel, subfamily J, member 11
kg	kilogram
BW	body weight
Kir6.2	gene locus for KCNJ11
KJHG	child and youth welfare law
l	litre
LDL	low-density lipoprotein
LGS	low-glucose suspend
m^2	square meters
max.	maximum
mg	milligram
micro	microalbuminuria
min.	minimum
avg.	average
MJ	megajoule
ml	millilitre
mm	millimetre
mmHg	millimetres of mercury = used to measure blood pressure
mmol	millimole
mon	month(s)
MODY	maturity onset diabetes of the young (adult diabetes in adolescents) = monogenetic diabetes
MRI	magnetic resonance imaging
n	number
NaCl	sodium chloride
NDM	neonatal diabetes mellitus
NCV	nerve conduction velocity
NPH insulin	neutral protamine Hagedorn insulin
NYHA	New York Heart Association classification system for the severity of heart failure
OGTT	oral glucose tolerance test
p	p-value/probability value – exceeding probability, statistical information
PAL value	physical activity level (value for measuring the daily physical activity expenditure)
Pat.	patient(s)
pCO_2	arterial partial pressure of carbon dioxide
pH	potentia hydrogenii (capacity of hydrogen) = negative logarithm of the hydrogen ion concentration/activity, measure for acidity of a medium
PLGM	predictive low glucose management
PNDM	permanent neonatal diabetes mellitus
RCT	randomized controlled trial
RR	Riva Rocci = arterial blood pressure, measured according to the method of Riva Rocci
s. c.	subcutaneous
SC	standard care (standard treatment)
SEARCH	search for diabetes in the youth study (studies for the identification of diabetes in children and adolescents)
SGB	German Social Code Book/Sozialgesetzbuch
SIGN	Scottish Intercollegiate Guidelines Network
sign.	significant
SSRI	selective serotonin reuptake inhibitor
STIKO	Standing Vaccination Commission of the Federal Republic of Germany/Ständige Impfkommission der Bundesrepublik Deutschland
SaP	sensor-augmented pump therapy
SUR 1	sulphonylurea receptor 1
SaT	sensor-augmented insulin therapy
T3	triiodothyronine
T4	thyroxine
daily	daily
tTG-IgA	tissue transglutaminase antibodies
Tg	thyroglobulin
TNDM	transient neonatal diabetes mellitus
TPO	thyroid peroxidase
TSHR	thyrotropin receptor
TRIGR	Trial to Reduce IDDM in the Genetically at the Risk (Study on the reduction of diabetes mellitus by immunodeficiency for genetical risks)
TSH	thyroid-stimulating hormone/thyrotropin
U	unit
UK	United Kingdom
esp.	especially
vs.	versus
WHO	World Health Organization
c. a.	condition after
CNS	central nervous system
ZnT8	zinc transporter 8

NOTICE OF UPDATE

The DDG clinical practice guidelines are updated regularly during the second half of the calendar year. Please ensure that you read and cite the respective current version.

Causes and background

The improvement of the care of children and adolescents with diabetes mellitus is an essential task of the Working Group for Paediatric Diabetology/Arbeitsgemeinschaft für Pädiatrische Diabetologie (AGPD).

In order to meet the needs of a chronic disease in childhood and adolescence, specific aspects of this stage of life must be taken into account.

These guidelines are addressed to all professional groups that care for and support children and adolescents with diabetes and their families, as well as to higher-level organisations (e. g. health insurance companies) that are involved with or affected by the disease.

In accordance with the specifications of the health ministers of the federal German states as well as the current practice of many clinics, these paediatric guidelines are valid until the age of up to 18 years. In individual clinical cases, however, these guidelines can also be extended to apply to early adulthood.

Epidemiology and types of diabetes in childhood and adolescence

Type 1 diabetes

Type 1 diabetes is still the most common metabolic disease in children. According to current estimates, 15600 to 17400 children and adolescents aged 0–14 years live with type 1 diabetes in Germany [Rosenbauer et al. 2013]. At the beginning of the millennium, 21000 to 24000 children and adolescents aged 0–19 years were affected [Rosenbauer et al. 2002]. This figure is currently estimated at around 30000 to 32000 [Rosenbauer et al. 2012].

In the 1990s, average annual new illness rates (incidence rates) were reported between 12.9 (95 % confidence interval 12.4–13.4) and 14.2 (95 % confidence interval 12.9–15.5) per 100000 children aged 0–14 years and 17.0 (95 % confidence interval 15.2–18.8) per 100000 children aged 0–19 years [Neu et al. 2001; Rosenbauer et al. 2002; Neu et al. 2008]. The incidence rate has increased by 3–4 % per year [Ehehalt et al. 2008; Neu et al. 2013]. Compared to the early 1990s, the new illness rate for 0–14-year-olds has now doubled and is currently 22.9 (95 % confidence interval 22.2–23.6). The increase in incidence rates especially affects the younger age groups.

Type 2 diabetes

Parallel to the increase in the prevalence of excess weight and obesity in childhood and adolescence [Kurth and Schaffrath 2007; Kromeyer-Hauschild et al. 2001], the incidence of type 2 diabetes has increased in this age group. Initial population-based estimates of type 2 in children and adolescents showed an incidence of 1.57 per 100000 in 2002 (95 % confidence interval 0.98–2.42) [Rosenbauer et al. 2003]. Studies carried out in Baden-Württemberg in 2004 showed that type 2 diabetes in Germany occurs in 0 to 20-year-olds with a prevalence of 2.3 per 100000 [Neu et al. 2005]. A second cross-sectional survey in Baden-Württemberg conducted in 2016 confirmed the relatively low and constant incidence of 2.4 per 100000 [Neu et al. 2017].

Risk factors, prevention and early detection of diabetes

According to the current guidelines of the International Pediatric Diabetes Association/Internationalen Pädiatrischen Diabetesgesellschaft ISPAD, the progression of type 1 diabetes has recently been divided into 4 stages [Couper 2018]. Stage 1, the beginning of type 1 diabetes according to the new classification, is when 2 or more diabetes-specific autoantibodies are detectable but children and adolescents are completely asymptomatic. If glucose tolerance is impaired, this corresponds to stage 2. Stage 1 and stage 2 can precede months and years of clinical manifestation. Stage 3 is when there is a manifestation and stage 4 is the case of a type 1 diabetic who has lived with the disease for some time.

Measures to maintain beta cell function can start before the onset of islet autoimmunity (early stage 1, primary prevention), after the development of autoantibodies but before clinical symptoms (stages 1 and 2) or rapidly after the manifestation of type 1 diabetes (stage 3). The progression of type 1 diabetes with proven autoantibodies occurs more rapidly with seroconversion to islet autoimmunity before the 3rd year of life and in children with an HLA-DR3/DR4-DQ8 genotype [Ziegler 2013]. The 5 and 10-year risk of type 1 diabetes manifestation in children who show multiple autoantibodies at the age of 5 years or earlier is 51 and 75 %, respectively [Danne et al., 2018], German Health Report Diabetes/Dt. Gesundheitsbericht Diabetes].

Type 1 diabetes

The diagnosis of type 1 diabetes is based on clinical symptoms and blood glucose monitoring. In case of doubt, further parameters can be used for diagnosis. These include:

1. Autoantibodies associated with diabetes (cytoplasmic islet cell antibodies [ICA], insulin autoantibodies [IAA], antibodies against glutamate decarboxylase [anti-GAD65], antibodies against tyrosine kinase IA-2 [anti-IA-2A], antibodies against zinc transporter-8 [anti ZnT8]),
2. An oral glucose tolerance test and
3. HbA1c determination [Ehehalt et al. 2010; Mayer-Davis EJ. 2018].

10–15 % of all children and adolescents under the age of 15 with type 1 diabetes have first-degree relatives with diabetes and thus a positive family history [Rosenbauer et al. 2003; Scottish Study Group for the Care of the Young Diabetic 2001]. The risk of developing diabetes is 3 times higher for children with a father suffering from diabetes than for children with a mother suffering from diabetes [Gale et al. 2001]. While antibodies and other markers might

provide a prediction and risk calculation regarding the occurrence of diabetes, there are no effective prevention strategies that could prevent the manifestation of diabetes [Rosenbloom et al. 2000; Australasian Paediatric Endocrine Group et al. 2005].

A general screening for type 1 diabetes should therefore not be performed in the general population or in high-risk groups among children and adolescents [Australasian Paediatric Endocrine Group et al. 2005]. According to the latest recommendations gleaned from scientific studies, screening and intervention in the absence of symptoms of type 1 diabetes remain reserved [Couper 2018].

Type 2 diabetes

An oral glucose tolerance test for the early detection of type 2 diabetes should be performed as of age 10 in cases of excess weight (BMI > 90th percentile) and the presence of at least 2 of the following risk factors:

- Type 2 diabetes in 1st or 2nd degree relatives,
- Belonging to a group with increased risk (e. g. East Asians, African Americans, Hispanics),
- Extreme obesity (BMI > 99.5th percentile) or
- Signs of insulin resistance or changes associated with it (arterial hypertension, dyslipidaemia, elevated transaminases, polycystic ovarian syndrome, acanthosis nigricans)

[Working Group for Obesity in Childhood and Adolescence/Arbeitsgemeinschaft Adipositas im Kindes- und Jugendalter AGA 2008].

Therapy for type 1 diabetes

Start of therapy

Insulin therapy should be initiated immediately after the diagnosis of type 1 diabetes, as the child's metabolism can deteriorate rapidly. A diabetes team experienced with children should be called in as soon as possible [Bangstad et al. 2007].

Therapy goals

Initial treatment and long-term care should be carried out by a team experienced in paediatric diabetology continuously from ages 1–18, and, in certain cases, also up to the age of 21. Specialised care has been shown to contribute to a reduction in days spent in hospital and readmissions, to a lower HbA1c value, better disease management and fewer complications [Cadario et al. 2009; Pihoker et al. 2014; Australasian Paediatric Endocrine Group et al. 2005].

The treatment of type 1 diabetes by the treatment team should include:

- Insulin therapy,
- Individual metabolic self-monitoring,
- Age-adapted structured training as well as
- Psychosocial care for the affected families.

The following medical goals are in the foreground when caring for paediatric patients with diabetes mellitus [Danne et al. 2014; Ziegler 2018]: avoidance of acute metabolic lapses, prevention of diabetes-related microvascular and macrovascular secondary diseases and normal physical development (growth in height, weight gain, onset of puberty). The patient's psychosocial development should be affected as little as possible by diabetes and its therapy, and integration and inclusion in day care, school and vocational training should be ensured.

Individual therapy goals should be formulated together with the child or adolescent and his or her family (HbA1c value, blood glucose target ranges, behavioural changes that come with risk-taking lifestyles, integration efforts, etc.).

The HbA1c target value of < 7.5 % was modified in 2018 by the ISPAD to a new target value of < 7.0 %, the American Diabetes Association (ADA) recommendations still lie at < 7.5 %, whereas the English National Institute for Health and Care Excellence (NICE) recommendations assume a target value of < 6.5 % [DiMeglio et al., 2018].

An additional parameter for evaluating the metabolic state is the time spent in the target range (TiR = time in range). Generally, the target range is defined as 70–180 mg/dl. An individual goal for the duration of the TiR is recommended [Danne 2017; Battelino T. 2019].

Preprandial glucose values should be between 70 and 130 mg/dl (4.0–7.0 mmol/l) and postprandial values between 90 and 180 mg/dl (5.0–10.0 mmol/l). Values of 80–140 mg/dl (4.4–7.8 mmol/l) are recommended at bedtime [DiMeglio 2018].

The average frequency of glucose control should be between 5 and 6 times a day but can be significantly higher in individual cases [Ziegler et al. 2011].

Continuous treatment of type 1 diabetes

The continuity of the treatment of diabetes mellitus of a child or adolescent with diabetes, both over time and during different phases of life and development, is decisive for ensuring a metabolic situation as close as possible to normoglycaemia and an unencumbered psychosocial development.

Care of children in day cares and schools

Children with diabetes should be cared for in day cares, regular schools and after-school centres [Hellems and Clarke 2007]. The right to inclusion is laid down in § 53 and § 54 of the German Social Code Book XII/Sozialgesetzbuch XII. This provides the basis for the assumption of costs for age-appropriate care.

An individual plan should be created for each institution which includes the frequency and intervention limits of blood glucose measurements, the delivery of insulin (mode, time, dose calculation), defining of mealtimes, symptoms and management of hypoglycaemias and hyperglycaemias [American Diabetes Association (ADA) 2015]. In addition to children, adolescents and their parents, all caregivers in the social environment must also be trained to enable inclusion [Ziegler 2018].

Support during the transition to young adulthood

The transition from paediatric to adult care affects young people with diabetes aged 16–21 years in a life phase of general upheaval and should therefore be accompanied. Various models (transitional consultations, structured paediatric/internal medicine transition, etc.) are in use [Nakhla et al. 2008; Australian Paediatric Endocrine Group et al. 2005; Court JM et al., 2008].

Care in case of illness and preventing illness risks

In the case of serious illnesses or in perioperative cases, children with diabetes should be referred to an experienced centre with well-trained staff, and the paediatric diabetologist should also be consulted [Brink et al. 2007].

Under no circumstances should insulin be completely omitted in the case of low glucose levels or refusal to eat. The administration of carbohydrates is necessary in order to avoid substrate deficiency and ketone body formation. The possibility of measuring β-hydroxybutyrate should be provided [Laffel 2018].

Children with diabetes mellitus should be vaccinated according to STIKO (Ständige Impfkommission/Standing Committee on Vaccination) recommendations.

Diabetes treatment during physical activity/sports

Regular exercise improves metabolic control and should be a matter of course for children and adolescents with diabetes. Regular swimming has been shown to significantly reduce HbA1c [Sideravicite et al. 2006].

Since blood glucose is lowered by energy consumption during physical activity, the risk of hypoglycaemia is increased. The strongest predictor for hypoglycaemia is the initial glucose value, which should be at least 120 mg/dl (6.6 mmol/l); otherwise additional carbohydrates may be required [Tansey et al. 2006]. Individual therapy plans with insulin dose adjustment and corresponding behavioural rules should be put together for each patient [Adolfsson 2018].

Insulin treatment

The standard treatment for paediatric patients with type 1 diabetes is intensified insulin therapy [Danne 2018].

All insulin therapy should be carried out as part of comprehensive diabetic care and with the support of the family.

Insulin therapy should be individually tailored to each child [Diabetes Control and Complications Trial Research Group 1995; White et al. 2008; Nathan et al. 2005; Musen et al. 2008].

Human insulin or insulin analogues should be used for paediatric patients [Bangstad et al. 2007; Danne et al. 2005; Mortensen et al. 2000; Deeb et al. 2001; Plank et al. 2005; Simpson et al. 2007].

Normal insulin should be used for intravenous insulin treatment.

Rapid-acting insulin and insulin analogues (prandial substitution)

There are differences between rapid-acting human insulin and fast-acting insulin analogues in the onset and duration of action in children and can be used flexibly for prandial substitution in children depending on the situation [Danne et al. 2005; Mortensen et al. 2000].

Rapid-acting insulin analogues should be used for insulin pump therapy.

Long-acting insulin and insulin analogues (basal substitution)

Both NPH insulin and long-acting insulin analogues can be used individually for basal insulin substitution in children [Danne et al. 2003; Danne et al. 2008; Thisted et al. 2006; Robertson et al. 2007; Danne et al. 2013; Thalange et al. 2015].

Insulin pump therapy

Insulin pump therapy for children and adolescents is both safe and effective. It has a positive effect on the frequency of hypoglycaemia, ketoacidosis and the metabolism [Karges et al., 2017]. Particularly in young children, pump therapy enables better adjustment of the insulin dose, especially at night, thus helping to prevent hypoglycaemias. Insulin pump therapy is recommended for the following indications:

- Small children, especially newborns, infants and preschoolers,
- Children and adolescents with a marked increase in blood glucose in the early morning hours (Dawn phenomenon),
- Severe hypoglycaemias, recurrent and nocturnal hypoglycaemias (despite intensified conventional therapy = ICT),
- HbA1c value outside target range (despite ICT),
- Severe blood glucose fluctuations, despite ICT, independent of the HbA1c value,
- Incipient microvascular or macrovascular secondary diseases,
- Limitation of the quality of life through previous insulin therapy
- Children with a great fear of needles,
- Pregnant adolescents (ideally before conception in the case of a planned pregnancy) as well as
- Competitive athletes [Phillip et al. 2007].

Continuous glucose monitoring (CGM), sensor-augmented insulin therapy (SaT) and sensor-augmented pump therapy (SaP)

CGM systems have been approved and can be prescribed for children and adolescents. They are available in the form of rt (real-time) CGM systems and in the form of isc (intermittent scanning) CGM systems. They can be used in combination with ICT (sensor-augmented insulin therapy = SaT). Some CGM systems can be used together with an insulin pump, or the insulin pump can serve as a monitor for CGM data. This combination (CSII + CGM) is now called sensor-augmented pump therapy (SaP). In addition, there is the possibility of switching off the basal rate when the tissue glucose reaches a critical limit (SaP + LGS = low-glucose suspend). A further development of the LGS already interrupts the supply of insulin if it predicts that hypoglycaemia will occur in the foreseeable future (predictive insulin switch-off, predictive low-glucose suspend = PLGS). The combination of both systems is called sensor-integrated pump therapy (SiP). Recently, CGM and insulin pumps have been combined to form an "AID system" (automated insulin delivery). An algorithm continuously calculates the respective insulin dose from the measured tissue glucose values, taking into account individual user data. Currently, "hybrid AIDs" are available for children and adolescents with type 1 diabetes. Here, the term "hybrid" means that the supply of the food-independent, basal insulin component takes place automatically according to the current insulin requirement and the insulin continues to be delivered manually by the user at mealtimes. All studies have shown that such hybrid AID systems can improve metabolic control in children, adolescents and adults with type 1 diabetes at night, but also during the day.

Soon, "Advanced AID Systems" will be available, which, in addition to adjusting the basal rate at higher glucose values, will automatically deliver small insulin microboli as an additional correction.

CGM should be used for children and adolescents with type 1 diabetes

- To reduce the hypoglycaemia rate (frequency, duration, depth) or
- In cases of recurrent nocturnal hypoglycaemia or
- In cases of a lack of hypoglycaemia perception or
- In cases of severe hypoglycaemia or
- To improve metabolic control without a simultaneous increase in hypoglycaemias or
- To reduce pronounced glucose variability

[Bergenstal et al. 2013; Ly et al. 2013; Maahs et al. 2014].

CGM should be used in paediatric patients with type 1 diabetes who have not achieved their HbA1c targets after having considered and used other measures and training courses for optimizing metabolic control [Battelino et al. 2012; Bergenstal et al. 2010; Danne 2017; Sherr 2018].

Nutritional recommendations

Nutritional counselling for children and adolescents with diabetes is an important part of a comprehensive therapy training plan and should include the following components:

- Information on the blood glucose efficacy of carbohydrates, fats and proteins,
- Strengthening healthy diets as part of family meals and in public institutions: regular, balanced meals and snacks (fruit, vegetables, raw vegetables), prevention of eating disorders (especially uncontrolled, binge eating) and the prevention of excess weight,
- Consideration of cultural eating habits,
- Enough energy for age-appropriate growth and development,
- Working toward a normal BMI, which includes regular physical activity,
- A good balance between energy intake and consumption in accordance with the insulin profiles,
- Nutrition during illness and sport and
- Reducing the risk of cardiovascular disease.

Nutrition specialists (dieticians/ecotrophologists) with an in-depth knowledge of paediatric and adolescent nutrition and insulin therapy should provide this counselling [Smart et al. 2014; Craig et al. 2011].

Nutritional recommendations should include all dietary components and their share in daily energy intake [German Nutrition Society/Deutsche Gesellschaft für Ernährung (DGE) 2015].

Diabetes training

Patient training is an essential part of diabetes therapy. It cannot be successful without proper, individualised medical treatment [Bloomgarden et al. 1987; de Weerdt et al. 1991].

Children, adolescents and their parents or other primary caregivers should have continuous access to qualified training starting from the time of diagnosis onwards [Craig et al. 2011; Bundesärztekammer (BÄK) et al. 2012; Canadian Diabetes Association Clinical Practice Guidelines Expert Committee 2013; Kulzer et al., 2013; Martin et al. 2012; Lange et al. 2014; Haas et al. 2014].

Training should be offered to caregivers in institutions (e. g. teachers in schools, educators in day cares, nurseries, after-school centres or group homes) [Hellems et al. 2007; Lange et al. 2012; Clarke et al. 2013].

The training should be conducted by a multi-professional diabetes team with proper knowledge of age-specific needs, possibilities and requirements that current diabetes therapies place on patients and their families.

All team members should participate in the training and work toward formulating and achieving uniform therapy concepts and goals [Swift et al. 2010; Lange et al. 2014; Cameron et al. 2013].

The learning process should be accompanied by evaluated training materials that are oriented towards the cognitive development and needs of children and adolescents. The same applies to training materials for parents which should include parenting tasks and age-specific diabetes therapy of their children [Martin et al. 2012; Lange et al. 2012; Lange et al. 2014].

Diabetic training is a continuous process and can only be successful through repeated needs-based offers (at least every 2 years) during long-term care. New therapy concepts, e. g. the start of insulin pump therapy or continuous glucose monitoring (CGM) and new life stages (e. g. starting school) should be accompanied by additional training. Other diseases (e. g. celiac disease or attention deficit/hyperactivity disorder ADHD) or acute complications (e. g. DKA, severe hypoglycaemias) or psychological problems require personalised treatment [Jacobson et al. 1997; Haas et al. 2014; Lange et al. 2014; Delamater et al. 2014].

Rehabilitation

In-patient rehabilitation can be carried out:

- In the case of persistently poor skills in dealing with diabetes,
- If there are diabetic secondary complications which are either already present or imminent in the short-term,
- After the in-patient primary therapy of the newly diagnosed diabetes mellitus if initial training cannot be provided near the patient's home (in the form of follow-up treatment),
- In the case of long-term inadequate metabolic control under out-patient care conditions, e. g. recurrent hypoglycaemia or ketoacidosis, and
- In the event of serious disruptions to activities and/or to the child or adolescent being able to participate in age-appropriate activities or in everyday life, e. g. frequent sick days (§ 4 SGB 9; Federal Working Group for Rehabilitation/Bundesarbeitsgemeinschaft Rehabilitation)

[Federal Working Group for Rehabilitation/Bundesarbeitsgemeinschaft für Rehabilitation (BAR) 2008; Fröhlich et al. 2008; German Pension Insurance Association/Deutsche Rentenversicherung Bund 2009; German Society for Paediatric Rehabilitation and Prevention/Deutsche Gesellschaft für pädiatrische Rehabilitation und Prävention 2007; Stachow et al. 2001].

Psychological and social risks, comorbidities and interventions

In the case of a diabetes diagnosis, a history of the psychosocial family situation should be recorded. The families should also re-

ceive psychosocial counselling and the interdisciplinary team should provide them with therapeutic aids for diabetes management. The psychological situation of the parents and other primary caregivers also needs be taken into account [Hürter et al. 1991; Sundelin et al. 1996; Delamater et al. 1990; Craig et al. 2011; Delamater et al. 2014; Forsander et al. 1998; Sullivan-Bolyai et al. 2011; Forsander et al. 2000; Zenlea et al. 2014].

The current psychosocial situation and possible stressful life events should be continuously recorded within the framework of long-term care (intellectual, academic, emotional and social development) and taken into account in therapy planning.

For this reason, it is important for social workers and psychologists with diabetes-specific expertise to be an integral part of the interdisciplinary diabetes team [Silverstein et al. 2005; Craig et al. 2011; de Wit et al. 2008; Delamater et al. 2014; Kulzer et al. 2013; Hilliard et al. 2011; Haas et al. 2014; de Wit et al., 2012].

Particularly in adolescents, signs of eating disorders and mood affective disorders (e. g. anxiety, depression, adjustment disorders) should be monitored and professional help sought and carried out in a timely manner.

If a psychiatrically-relevant disorder is present, paediatric and adolescent psychiatrists or psychological psychotherapists should be consulted in order to initiate co-treatment if necessary. A coordinated treatment between psychiatrist and diabetes team should be strived for [Northam et al. 2005; Lawrence et al. 2006; Delamater et al. 2014; Kulzer et al. 2013; Young et al. 2013].

Children and adolescents with diabetes have an increased risk of impaired information processing and learning. Children with early onset diabetes, severe hypoglycaemias and chronic hyperglycaemias in early life are particularly affected.

Therefore, the school performance of children with increased risk (diabetes diagnosis under 5 years, severe hypoglycaemias/chronic hyperglycaemias) should be recorded. In case of learning difficulties, they, just as all children, should be assessed neuro-physiologically and psychologically and, if necessary, receive educational support [Delamater et al. 2014].

Acute complications

Diabetic ketoacidosis

Diabetic ketoacidosis is a potentially life-threatening disease. It should be treated immediately in a specialized facility by a diabetes team experienced with children. There should be a written treatment plan for treating diabetic ketoacidosis in children and adolescents [Australasian Paediatric Endocrine Group et al. 2005; Glaser et al. 2006; Fiordalisi et al. 2007].

The biochemical criteria for ketoacidosis include:

- pH < 7.3,
- Bicarbonate < 15 mmol/l,
- Hyperglycaemia > 11 mmol/l, > 200 mg/dl and
- Ketonuria and presences of ketones in serum.

Ketoacidosis is categorised into 3 stages of severity:

- Mild (pH < 7.3; bicarbonate < 15 mmol/l),
- Moderate (pH < 7.2; bicarbonate < 10 mmol/l) and
- Severe (pH < 7.1; bicarbonate 5 mmol/l) [Wolfsdorf et al. 2007].

The following therapy goals are to be pursued in ketoacidosis:

- Stabilisation of the cardiovascular system with initial volume bolus using isotonic solution,
- Subsequent slow, balanced fluid resuscitation and electrolyte replacement,
- Slow normalization of blood glucose,
- Balancing out of acidosis and ketosis,
- Avoidance of therapy complications (cerebral oedema, hypokalaemia, hypophosphatemia) and
- Diagnosis and therapy of triggering factors

[Australasian Paediatric Endocrine Group et al. 2005b; Wolfsdorf et al. 2018] (▶ **Table 1**).

During the treatment of severe diabetic ketoazidoses, clinical observation and monitoring should take place at least every hour [Australasian Paediatric Endocrine Group 2005; Edge et al. 2006; Wolfsdorf et al. 2018].

Patients with severe ketoacidosis and an increased risk of cerebral oedema should be treated immediately in an intensive care unit or a specialized diabetes unit with comparable equipment by a diabetes team experienced with children.

Patients with suspected cerebral oedema should be treated in an intensive care unit in cooperation with an experienced diabetes team [Australasian Paediatric Endocrine Group et al. 2005; Wolfsdorf et al. 2018].

Patients with clear signs of cerebral oedema should be treated with mannitol or hypertonic saline solution before further diagnostic measures (MRI) are initiated [Australasian Paediatric Endocrine Group et al. 2005; Fiordalisi et al. 2007; Hanas et al. 2007; Roberts et al. 2001; Franklin et al. 1982; Banks et al. 2008; Wolfsdorf et al. 2018].

Case reports or case series are available on the therapeutic efficacy in symptomatic cerebral oedema of an early intravenous mannitol administration (0.5–1 g/kg) over 10–15 min and repeated if necessary (after 30 min.) [Fiordalisi et al. 2007; Hanas et al. 2007; Roberts et al. 2001; Franklin et al. 1982].

Hypoglycaemia

Hypoglycaemia is the most common acute complication in diabetes [Diabetes Control and Complications Trial Research Group 1994].

According to the latest recommendation by the Hypoglycaemia Study Group [International Hypoglycaemia Study Group 2017], a distinction is made between blood glucose values into the following:

Stage 1: < 70 mg/dl (3.9 mmol/l), requires attention and treatment, if necessary

Stage 2: < 54 mg/dl (3 mmol/l), always requires immediate treatment and

Stage 3: with impaired consciousness, always requires immediate treatment.

Slight hypoglycaemia can be corrected by the patient through the intake of fast-acting carbohydrates.

▶ **Table 1** Medicinal treatment of ketoacidosis (taking the control of electrolytes, pH, blood glucose, ketone bodies into consideration).

Treatment goal/ indication	Medicine	Dose	Chronological sequence
Initial stabilisation of cardiovascular system, if necessary	NaCl 0.9 %	10–20 ml/kg IV	Immediately over 1–2 h
Fluid resuscitation after initial cardiovascular stabilisation	NaCl 0.9 % or Ringer's solution, after 4–6 h NaCl 0.45 % also possible	Maximum daily IV dose < 1.5 to 2 times the maintenance requirement in relation to age/weight/body	At least over 36–48 h
Lowering of blood glucose	Normal insulin	0.1 U/kg/h IV, for younger children 0.05 U/kg/h	Begin insulin administration 1–2 h after start of volume administration; no interruption of insulin delivery up to pH > 7.3; lowering of blood glucose by 2–5 mmol/l/h (36–90 mg/dl/h)
Avoidance of hypoglycaemia	Glucose	Final concentration: 5 % glucose/0.45 % NaCl solution	Start from BG as of 15 mmol/l (270 mg/dl) or at lowering of BG > 5 mmol/l/h (90 mg/dl/h)
Balance of potassium	KCl	40 mmol/l volume; 5 mmol/kg/day IV; not > 0.5 mmol/kg/h	For hypokalaemia immediately, for normokalaemia together with the start of insulin administration, in the case of hyperkalaemia only after resumption of urine production; continuous administration until volume compensation has been fully compensated
Balance of phosphates	Potassium phosphate	At pH < 7.1 half the potassium substitution as potassium phosphate	Until phosphate is in the normal range again

NaCl: Sodium chloride; BG: Blood glucose; KCl: Potassium chloride, IV: intravenously, U: unit, h: hour.

Severe hypoglycaemia can only be remedied with external help due to the accompanying limitation or loss of consciousness. In addition to a loss of consciousness, a severe hypoglycaemia can also be accompanied by a cerebral seizure.

Children and adolescents with type 1 diabetes should always carry fast-acting carbohydrates in the form of dextrose or the like, in order to be able to act immediately in the event of mild hypoglycaemia and thus prevent severe hypoglycaemia. Parents or other primary caregivers should be instructed in the use of glucagon injections or other immediate measures.

Caregivers in e. g. day cares and day care centres, and teachers in schools should also receive instruction on the risks and treatment options for hypoglycaemia.

In the case of hypoglycaemia perception disorder, a higher blood glucose level should be temporarily set [Australasian Paediatric Endocrine Group et al. 2005; Clarke et al. 2008]. The use of a CGM system with hypoglycaemia suspend should also be considered.

Long-term complications and preventive examinations (screening)

The HbA1c value should be determined at least every 3 months to check metabolic control [Diabetes Control and Complications Trial Research Group 1994; Nathan et al. 2005; White et al. 2008]. All other long-term controls are listed in ▶ **Table 2**.

Associated autoimmune diseases

Diagnostics and therapy of thyroid diseases

In children and adolescents with diabetes, determination of the thyroid-stimulating hormone (TSH) and determination of thyroid autoantibodies (antibodies against thyroid peroxidase [TPOAb] and thyroglobulin [TgAb]) should be performed upon diabetes manifestation and at regular intervals of 1–2 years or with associated symptoms [Australasian Paediatric Endocrine Group et al. 2005; Bangstad et al. 2007; Silverstein et al. 2005; Kordonouri et al. 2011].

If TPO autoantibodies and/or a TSH increase are present, a sonography of the thyroid should be performed.

For the therapy of autoimmune hypothyroidism or struma, L-thyroxine should be used according to the therapy plan (▶ **Fig. 1**)

Diagnostics and therapy of celiac disease

Children and adolescents with diabetes are to be examined for celiac disease in the event of diabetes manifestation and at intervals of 1–2 years and in the case of associated symptoms [Australasian Paediatric Endocrine Group et al. 2005; Hill et al. 2005; Silverstein et al. 2005; Kordonouri et al. 2007; Kordonouri et al. 2014; Kordonouri et al. 2011].

In cases of confirmed celiac disease (serologic and bioptic) with symptoms or extraintestinal manifestation, a gluten-free diet should be followed [Hansen et al. 2006; Amin et al. 2002; Hill et al. 2005; Lewis et al. 1996; Kordonouri et al. 2011].

According to the latest recommendations, a biopsy can be dispensed with in the case of clear clinical symptoms, high anti-tissue transglutaminase (anti-TG2) immunoglobulin A (IgA) autoantibodies (> 10 times above norm) and endomysium antibodies as well as a positive HLA-DQ2 or DQ8 haplotype [Mahmud 2018]. However, this recommendation is inconsistent with other guidelines. As most children with type 1 diabetes and positive tTG-Ab are asymptomatic, a biopsy is still frequently required to confirm the diagnosis.

In asymptomatic patients, the indication for a gluten-free diet or further follow-up should be carried out in cooperation with the paediatric gastroenterologist.

▶ **Table 2** Long-term complications: screening examinations and interventions.

Screening examination and intervals	Recommended screening method(s)	Interventions
1. **Retinopathy:**		
▪ Every 1–2 years; ▪ From age 11 or as of 5 years of diabetes	Binocular bi-microscopic funduscopy in mydriasis by experienced ophthalmologist	▪ Improvement of glycaemic control ▪ Normalise blood pressure ▪ Normalise dyslipidaemia ▪ Laser therapy ▪ Intravitreal injections
2. **Nephropathy:**		
▪ Annually; ▪ From age 11 or as of 5 years of diabetes	Detection of microalbuminuria: ▪ Concentration measurement: 20–200 mg/l ▪ Albumin excretion rate > 20 to < 200 µg/min ▪ Albumin-creatinine ratio ▪ 24-hour urine collection, if necessary	▪ Improvement of glycaemic control ▪ For hypertension + microalbuminuria: ▪ ACE inhibitors ▪ AT-1 blockers ▪ Persistent microalbuminuria without hypertension: consider ACE inhibitors ▪ Nicotine abstinence
3. **Nephropathy:**		
▪ Annually, for long-term poor metabolic condition from age 11 or as of 5 years of diabetes	▪ Medical examination ▪ Tactile sensitivity (aesthesiometer) ▪ Vibration sensitivity (tuning fork test) ▪ Testing reflexes	▪ Improvement of glycaemic control
4. **Hypertension:**		
▪ Every 3 months and, as of age 11, annually at minimum	▪ Resting blood pressure ▪ 24-hour blood pressure at minimum 2 × > 95th percentile or microalbuminuria	▪ Lifestyle intervention (exercise, salt reduction, weight reduction, reduction of alcohol and/or nicotine) ▪ If not successful: ACE inhibitors; for contraindications or side effects: AT-1 blockers; combination with other drugs if required
5. **Hyperlipidaemia:**		
▪ Within the first year of diagnosis ▪ Then every 2 years ▪ Before puberty every 5 years	Detection of ▪ Total cholesterol ▪ HDL cholesterol ▪ LDL cholesterol ▪ Triglycerides	▪ Dietary therapy ▪ If not successful: statins from age 8 Statins

ACE: angiotensin converting enzyme; AT: angiotensin; HDL: High-density lipoprotein; LDL: Low-density lipoprotein.

Other forms of diabetes in childhood and adolescence

Type 2 diabetes

Type 2 diabetes in adolescents should be diagnosed according to the limits for fasting glucose and oral glucose tolerance test (OGTT) using the standard or reference method.

If the following limit values are exceeded, the result in asymptomatic patients must be confirmed by a second test on a different day:

- Fasting glucose: > 126 mg/dl (> 7.0 mmol/l) and
- OGTT: 2 h value > 200 mg/dl (> 11.1 mmol/l) [Genuth et al. 2003].

Additional laboratory tests can provide information on the differentiation between type 2 diabetes and type 1 diabetes:

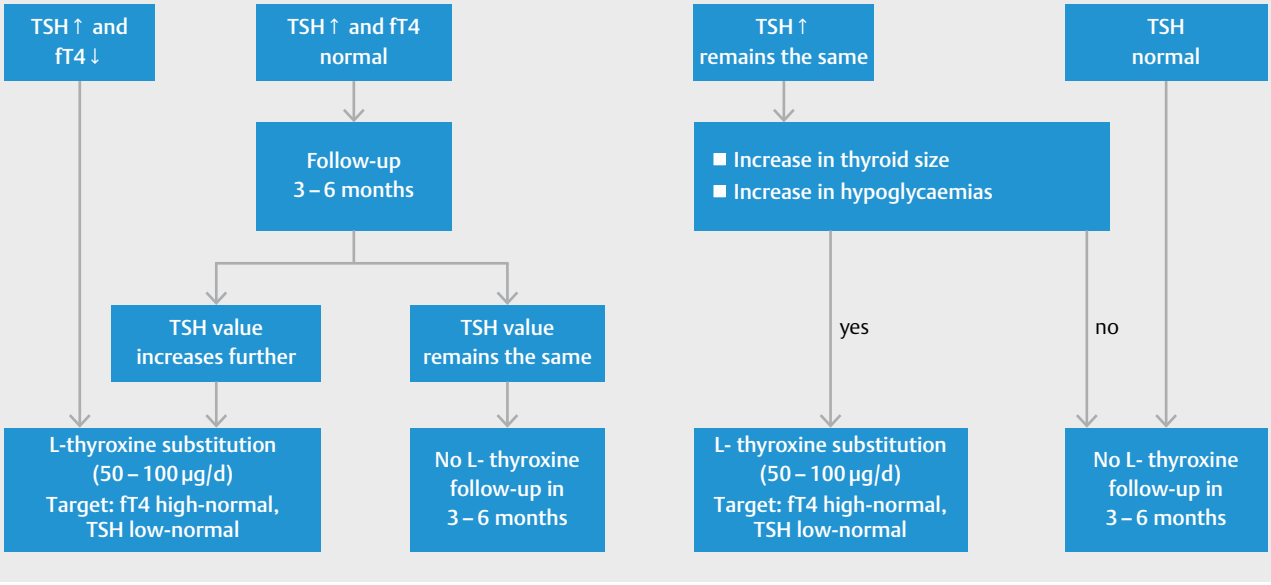
- C-peptide and
- Diabetes-specific autoantibodies (GAD, IA-2, ICA, IAA, ZnT8) [Alberti et al. 2004; Genuth et al. 2003].

In the treatment of type 2 diabetes in adolescents (▶ **Fig. 2**) [Alberti et al. 2004]), the target fasting glucose should be < 126 mg/dl and the target HbA1c value should be < 7 % [Zeitler et al. 2014; UK Prospective Diabetes Study (UKPDS) Group 1998; Holman et al. 2008].

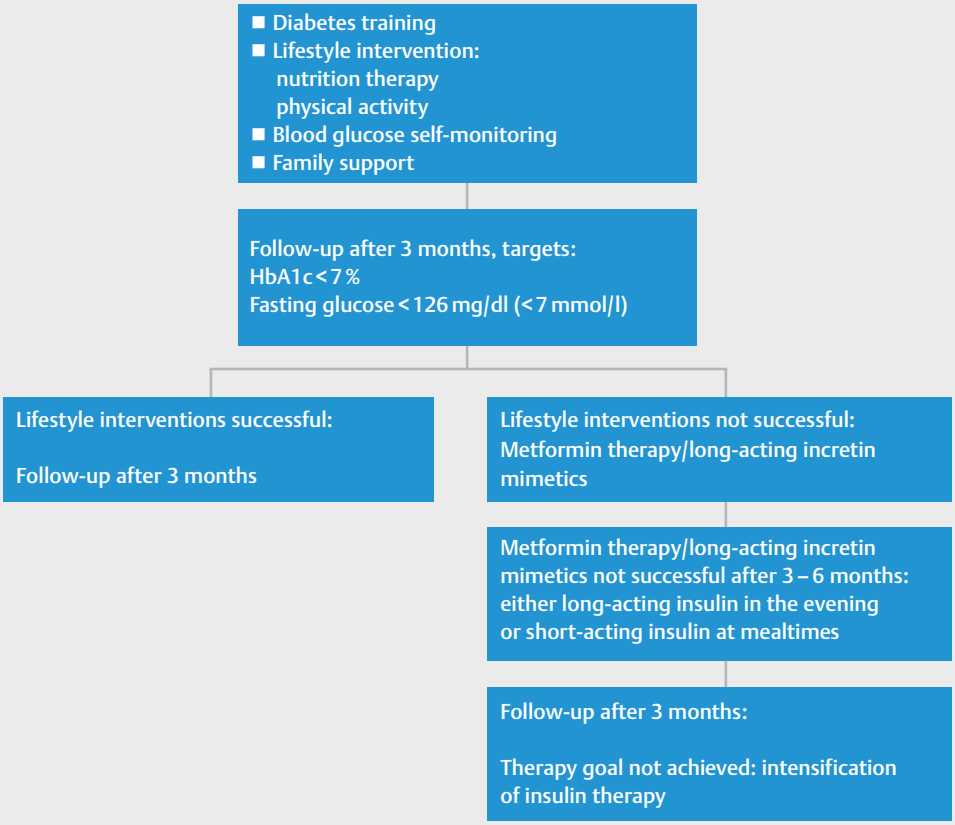
Training for adolescents with type 2 diabetes should include nutritional counselling and guidance on physical activity as part of a structured obesity programme [Reinehr et al. 2007; Working Group for Obesity in Childhood and Adolescence/Arbeitsgemeinschaft Adipositas im Kindes- und Jugendalter (AGA) 2008].

In addition, individually tailored modular training for type 2 diabetes should take place using the relevant contents from the type 1 diabetes training.

At a starting HbA1c value of ≥ 9 % or spontaneous hyperglycaemia ≥ 250 mg/dl and with signs of absolute insulin deficiency (ketonuria, ketoacidosis), an initial insulin therapy should be started. In all other cases, metformin is the first drug of choice for drug therapy in children and adolescents [Shimazaki et al. 2007; UK Prospective Diabetes Study (UKPDS) Group 1998; Jones et al. 2002; Gottschalk et al. 2007; Zeitler et al. 2014]. As of recently, long-acting incretin mimetics can also be used in childhood and adolescence in addition to metformin [7].



▶ **Fig. 1** Diagram for treating Hashimoto's thyroiditis. Source: Diagnosis, Therapy and Follow-Up of Diabetes Mellitus in Children and Adolescents. S3-Guideline of the DDG and AGPD 2015. German Association of the Scientific Medical Professional Societies/AWMF registration number 057–016 [rerif]. TSH: thyroid-stimulating hormone; fT4: free thyroxine.



▶ **Fig. 2** Diagram for treating type 2 diabetes in children and adolescents Source: Diagnosis, Therapy and Follow-Up of Diabetes Mellitus in Children and Adolescents. S3-Guideline of the DDG and AGPD 2015. German Association of the Scientific Medical Professional Societies/AWMF registration number 057–016 [rerif].

▶ **Table 3** The most common MODY forms and their clinical characteristics.

MODY type (international share in percent); heredity	Age (Y) at manifestation	Severity of hyperglycaemia	Clinical picture
HNF1A-MODY (MODY3) HNF-1α-(20–50 %) autosomal dominant	14 (4–18)	Severe hyperglycaemia	▪ Strong increase of BG in OGTT (> 90 mg/dl), low renal threshold (frequent glucosuria in BG values) < 180 mg/dl (< 10 mmol/l)) ▪ Increasing hyperglycaemia with age ▪ Response to sulfonylureas/glinides
GCK-MODY (MODY2) Glucokinase (20–50 %) autosomal dominant	10 (0–18)	Mild hyperglycaemia	▪ Often by chance ▪ Fasting BG slightly increased between 99 and 144 mg/dl (5.5–8 mmol/l) ▪ BG increase in the OGTT low (by < 63 mg/dl or < 3.5 mmol/l) ▪ No BG deterioration in old age ▪ Rarely microvascular or macrovascular complications, even without drug therapy
HNF4A-MODY (MODY1) HNF-4α-(1–5 %) autosomal dominant	17 (5–18)	Significantly hyperglycaemic	▪ Similar to HNF-1α, but renal threshold normal ▪ Response to sulfonylureas

MODY: Maturity onset diabetes of the young; HNF-1α: hepatic nuclear factor 1 alpha; BG: blood glucose; OGTT: oral glucose tolerance test; HNF-4α: hepatic nuclear factor 4 alpha.

Monogenetic diabetes

A molecular genetic diagnosis of the most common MODY forms can be recommended in cases of justified assumptions because of its importance for therapy, long-term prognosis and genetic counselling of families [Hattersley et al. 2006; Ellard et al. 2008] (▶ **Table 3**).

Before the affected genes are sequenced, counselling and information must be provided in accordance with the Gene Diagnostics Act, especially on the right to knowledge and ignorance of genetic information [Murphy et al. 2008; McDonald and Ellard 2013; Ellard et al. 2008; Badenhoop et al. 2008; Gene Diagnostics Act 2009].

Neonatal diabetes mellitus (NDM)

A special form of genetic diabetes is neo-natal diabetes mellitus (NDM) and diabetes that manifests within the first 6 months of life. Clinically, they are classified into 2 subgroups: transient (TNDM) and permanent (PNDM) neonatal diabetes mellitus. For diagnosis of neonatal diabetes or diabetes manifestation up to and including the sixth month of life, see the box "Neonatal diabetes – diagnostic procedure".

NEONATAL DIABETES – DIAGNOSTIC PROCEDURE

Diagnostic procedure for diabetes manifestation up to the 6th month of life, if necessary up to the 1st year of life

1. Exclusion of pancreatic insufficiency
   - Sonography to rule out pancreatic aplasia
   - Determination of elastase in faeces to exclude exocrine insufficiency
2. If sonography is unremarkable or not assessable:
   - Determination of diabetic autoantibodies (GAD, IA-2, ICA, IAA, ZnT8)
3. If sonography is unremarkable or not assessable, autoantibodies negative and elastase in stool without findings, a molecular genetic analysis should be carried out promptly because of the high therapeutic relevance for the differential diagnosis of:
   - Anomalies of chromosome 6q24 (TNDM)
   - Mutations of the KCNJ11 gene (PNDM, TNDM)
   - Mutations of the ABCC8 gene (PNDM, TNDM)
   - Mutations of insulin gene (PNDM)
4. For reduced elastase in stool and negative molecular genetic analysis for chromosome 6q24, KCNJ11, ABCC8 and insulin gene as well as negative or positive autoantibodies:
   - Examination for rare genetic diseases/genetic syndromes

In the case of etiologically unexplained neonatal diabetes mellitus and diabetes mellitus, which manifests itself up to the 6th month of life, a molecular genetic analysis should be performed as early as possible in order to start appropriate therapy for sulfonylurea-sensitive mutations as early as possible [Flanagan et al. 2006; Babenko et al. 2006; Klupa et al. 2008; Battaglia et al. 2012; Shah et al. 2012].

In most cases, insulin therapy is administered first if neonatal diabetes is present. Under in-patient conditions and tight controls, an initial therapy attempt with sulfonylureas may be useful if the result of the molecular genetic examination is expected shortly. In the presence of a mutation of the KCNJ11 or the ABCC8 gene, therapy with sulfonylureas should be attempted as early as possible [Hattersley et al. 2006; Pearson et al. 2006; Mlynarski et al. 2007; Koster et al. 2008; Slingerland et al. 2008; Thurber et al.].

Diabetes in cystic fibrosis

Since diabetes in cystic fibrosis is often clinically difficult to detect, children with cystic fibrosis as of age 10 should receive an oral glucose tolerance test annually [Lanng et al. 1994]. New studies show better results using CGM to detect glucose variability [Chan 2018].

With a confirmed diagnosis of diabetes, early treatment of cystic fibrosis-related diabetes (CFRD) should be initiated [Nousia-Arvanitakis et al. 2001; Rolon et al. 2001; Lanng et al. 1994; Dobson et al. 2002; Frost et al., 2018].

Insulin is to be used for long-term therapy of CF-related diabetes, however within the first 12 months after diagnosis, a therapy attempt with glinides or sulphonylureas may be undertaken [Ballmann et al. 2014; O'Riordan et al. 2008].

If cystic fibrosis is present, a high-calorie, high-fat diet should also be followed after the diagnosis of diabetes. Calorie reduction is contraindicated [O'Riordan et al. 2008].

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Conflict of Interest

TK held lectures for Lilly on the topic of severe hypoglycaemia.

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The literature is available online from [8] ff.