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

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## INDEX OF ABBREVIATIONS

| Abbreviation | Description (German designation, if applicable) |
|---|---|
| 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 | German Association for Obesity in Childhood and Adolescence (Arbeitsgemeinschaft Adipositas) |
| AGPD | German Pediatric Diabetology Association (Arbeitsgemeinschaft für pädiatrische Diabetologie) |

| | |
|---|---|
| AHCPR | Agency for Health Care Policy and Research |
| AIHA | Autoimmune hemolytic anemia |
| Ab | Antibodies |
| ALAT | Alanine aminotransferase = liver enzyme |
| APS | German Association for Pediatric Metabolic Disorders (Arbeitsgemeinschaft für pädiatrische Stoffwechselstörungen) |
| APS | Autoimmune polyglandular syndrome |
| AT1 | blocker Angiotensin type 1 receptor blocker |
| AWMF | Scientific Medical Society Board |
| BABYDIAB | German BabyDiab study |
| BAR | German Federal Association for Rehabilitation |
| BdKJ | German Diabetic Children and Adolescents' Association |
| BG | Blood glucose |
| BMI | Body mass index |
| BMI-SDS | Body mass index standard deviation score (standardized body mass index) |
| 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 |
| DCC | Trial Diabetes Control and Complications Trial |
| DDG | German Diabetes Society (Deutsche Diabetes Gesellschaft) |
| DEND | Diabetes epilepsy and neurological delay |
| DENIS | German Nicotinamide Intervention Study |
| DEPS-R | Diabetes Eating Problem Survey—Revised |
| DGE | German Society for Nutrition (Deutsche Gesellschaft für Ernährung) |
| DGEM | German Society for Nutritional Medicine (Deutsche Gesellschaft für Ernährungsmedizin) |
| DGKJP | German Society for Child and Adolescent Psychiatry, Psychomatics and Psychotherapy (Deutsche Gesellschaft für Kinder- und Jugend- psychiatrie, Psychosomatik und Psychotherapie) |
| diab | Diabetic |
| Diabetes | DE Diabetes-dedicated organization |
| DIAMYD | Diamyd® study |
| DIPP | Diabetes Prediction and Prevention Project |
| DKA | Diabetic ketoacidosis |
| dl | Deciliters |
| DNSG | Diabetes and Nutrition Study Group |
| DPT-1 | Diabetes Prevention Trial—Type 1 |
| DPV | Diabetes Patient Administration |
| EASD | European Association for the Study of Diabetes |
| EDIC | Trial Epidemiology of Diabetes Interventions and Complications Trial = successor to the DCC trial |
| EIF2AK3 gene | Gene site for mutations which lead to a genetic syndrome with diabetes |
| EC | Evidence class (methodological quality of a study according to criteria from evidence-based medicine) |
| ECG | Electrocardiogram |
| EMA | European Medicines Agency |
| ENDIT | European Nicotinamide Intervention Trial |
| ES | Educational support |
| ethn. | Ethnic |
| fam | Family |
| FES | Family Environment Scale = scale for assessment of the social characteristics and environment of families |
| FOXP3 gene | Gene site for mutations which lead to genetic syndromes with diabetes |
| FST-D | Family system therapy for patients with diabetes |
| fT3 | Free triiodothyronine |
| fT4 | Free thyroxine |
| g | Grams |
| GAD | Glutamate decarboxylase |
| GCK | Glucokinase |
| h | Hour |
| HbA1c | Glycolized hemoglobin |
| HDL | High-density lipoprotein |
| HHS | Hyperosmolar hyperglycemic state |
| HLA | Human leucocyte antigen |
| HNF | Hepatocyte nuclear factor |
| HTA | Health technology assessment = systematic assessment of medical technologies, procedures, and aids, but also organization structures in which medical services are provided |
| IU | International unit(s) |
| i.m. | Intramuscular |
| i. v. | Intravenous |
| IA2 | Tyrosine phosphatase IA2 antibodies |
| IAA | Insulin autoantibodies |
| ICA | Islet cell antibodies |
| ICT | Intensified conventional therapy |
| IgA | Immunoglobulin A |
| IgG | Immunoglobulin G |
| INS | Insulin (gene) |
| IPEX syndrome | Immunodysregulation polyendocrinopathy enteropathy X-linked syndrome und Immundysregulation) |
| IPF-1gene | Insulin promotor factor 1 gene = gene site for mutations which lead to MODY-4 diabetes |

| | |
|---|---|
| IRMA | Intraretinal microvascular anomaly |
| ISPAD | International Society for Pediatric and Adolescent Diabetes |
| ITP | Immune thrombocytopenic purpura |
| y | Years |
| n.s. | Not specified |
| kcal | Kilocalories |
| KCNJ11 | Inward-rectifier potassium channel, subfamily J, member 11 |
| kg | Kilograms |
| BW | Body weight |
| Kir6.2 | Gene localization for KCNJ11 |
| KJHG | German Child and Youth Welfare Law (Kinder- und Jugendhilfegesetz) |
| l | Liters |
| LDL | Low-density lipoprotein |
| LGS | Low-glucose suspend |
| $m^2$ | Square meters |
| max. | Maximum |
| mg | Milligrams |
| Micro | Microalbuminuria |
| min. | Minimum |
| avg. | average |
| MJ | Megajoules |
| ml | Milliliters |
| mm | Millimeters |
| mmHg | Millimeter of mercury = unit of measure for blood pressure |
| mmol | Millimol |
| Mo | Month(s) |
| MODY | Maturity onset diabetes of the young = monogenic diabetes |
| MRI | Magnetic resonance imaging |
| n | Number |
| NaCl | Sodium chloride |
| NDM | Neonatal diabetes mellitus |
| NLG | Nerve conduction velocity |
| NPH | insulin Neutral protamine Hagedorn insulin |
| NYHA | New York Heart Association = classification system by the New York Heart Association for severity of heart failure |
| OGTT | Oral glucose tolerance test |
| p | p-Value = Overshoot probability, statistical indication |
| PAL value | Physical activity level (value for measuring physical performance) |
| Pat. | Patient(s) |
| pCO2 | Arterial carbon dioxide partial pressure |
| pH | potential of hydrogen = negative common logarithm for hydrogen ion activity, measure of a medium's acidity |
| PLGM | Predictive low-glucose management |
| PNDM | Permanent neonatal diabetes mellitus |
| RCT | Randomized controlled trial |
| RR | Riva Rocci = arterial pressure, measured acc. to the Riva Rocci method |
| s.c. | subcutaneous |
| SC | Standard care |
| SEARCH | Search for diabetes in the youth study |
| SGB | German Penal Code (Strafgesetzbuch) |
| 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) |
| SUR 1 | Sulfonylurea receptor 1 |
| T3 | Triiodothyronine |
| T4 | Thyroxine |
| dly | daily |
| Tg-Ab | Thyroglobulin antibodies |
| TNDM | Transient neonatal diabetes mellitus |
| TPO-Ab | Thyroid peroxidase antibodies |
| TRAK | TSH receptor autoantibodies |
| TRIGR | Trial to Reduce IDDM in the Genetically at the Risk |
| TSH | Thyroid-stimulating hormone/thyrotropin |
| U | Unit |
| UK | United Kingdom |
| esp. | especially |
| vs. | versus |
| WHO | World Health Organization |
| CNS | Central nervous system |
| ZnT8 | Zinc transporter 8 |

# 1 Matter and Background

The improvement in care for children and adolescents with diabetes mellitus is an integral task for the German Pediatric Diabetology Association (AGPD).

In order to take the particularities of a chronic childhood and youth disease into account, specific aspects of this stage of life must be considered.

These recommendations apply to all professions involved in the management and support of children and adolescents with diabetes and their families, as well as superordinate organizations (e. g., health insurance providers) that deal with the disease.

According to the standards by federal state health ministers and the common practice of many clinics, the age up to which these pediatric guidelines should apply is defined as 18 years of age. These guidelines can also apply to young adults, however.

# 2 Epidemiology and Types of Diabetes in Childhood and Adolescence

## 2.1 Type 1 diabetes

Type 1 diabetes remains the most common metabolic childhood disease. According to current estimates, between 15,600 and

17,400 children up to 14 years of age with type 1 diabetes live in Germany [Rosenbauer et al. 2013]. In the age group of 0 to 19 years, between 21,000 and 24,000 children and adolescents were affected at the start of the millennium [Rosenbauer et al. 2002]. This figure is currently estimated to be around 30,000 to 32,000 [Rosenbauer et al. 2012].

In the 1990s, the average annual incidence rate was reported as between 12.9 (95 % confidence interval [CI] 12.4–13.4) and 14.2 (95 % CI 12.9–15.5) per 100,000 children aged 0 to 14 years and 17.0 (95 % CI 15.2–18.8) per 100,000 aged 0 to 19 years [Neu et al. 2001; Rosenbauer et al. 2002b; Neu et al. 2008]. The incidence rate rises by 3–4 % annually [Ehehalt et al. 2008; Neu et al. 2013]. Compared to the early 1990s, the incidence rate for 0- to 14-year-olds has now doubled and is currently 22.9 % (95 % CI 22.2–23.6). The rise in incidence can be observed particularly among younger age groups.

### 2.2 Type 2 diabetes

In parallel to the rise in prevalence of overweight and obesity in children and adolescents [Kurth et al. 2007; Kromeyer-Hauschild et al. 2001], the frequency of type 2 diabetes has increased in this age group. Initial population-based estimates of type 2 diabetes in children and adolescents in 2002 yielded an incidence rate of 1.57 per 100,000 (95 % CI 0.98–2.42) [Rosenbauer et al. 2003]. Investigations in Baden-Württemberg from 2004 indicated that among 0- to 20-year-olds in Germany, type 2 diabetes exhibits a prevalence of 2.3 per 100,000 [Neu et al. 2005]. The current incidence is estimated at 200 new cases per year among 12- to 19-year-olds [Danne 2014].

## 3 Risk Factors, Prevention, and Early Detection of Diabetes

### 3.1 Type 1 diabetes

The diagnosis of type 1 diabetes is based on clinical symptoms and blood glucose testing. In cases of doubt, further parameters for diagnosis clarification may be employed. These include: 1) autoantibodies associated with diabetes (ICA, GAD 65, IA2, IAA, ZnT8), 2) oral glucose tolerance test, and 3) HbA1c determination [International Society for Pediatric and Adolescent Diabetes (ISPAD) 2014; Ehehalt et al. 2010].

Among all children and adolescents under 15 years of age with type 1 diabetes, 10–15 % have first-degree relatives with diabetes and thus a positive familial medical history [Rosenbauer et al. 2003; Scottish Study Group for the Care of the Young Diabetic 2001]. The risk of developing diabetes is three times higher for a child with a diabetic father than for a child with a diabetic mother [Gale and Gillespie (2001)]. While antibodies and other markers allow prediction and risk calculation with regard to the development of diabetes, there is a lack of effective strategies that could prevent diabetes onset [Rosenbloom et al. 2000; Australasian Paediatric Endocrine Group et al. 2005].

General screening for type 1 diabetes should therefore not be carried out in the general population or in high-risk groups among children and adolescents [Australasian Paediatric Endocrine Group et al. 2005b].

### 3.2 Type 2 diabetes

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

- type 2 diabetes among first- or second-degree relatives
- belonging to a higher-risk ethnic group (e. g., East Asian, African American, Hispanic)
- extreme obesity (BMI > 99.5th percentile)
- signs of insulin resistance or associated changes (arterial hypertension, dyslipidemia, elevated transaminases, polycystic ovary syndrome, acanthosis nigricans)

[Arbeitsgemeinschaft Adipositas im Kindes- und Jugendalter (AGA) (2008)]

## 4 Treatment of Type 1 Diabetes

### 4.1 Start of the therapy

Insulin therapy should be introduced immediately upon diagnosis of type 1 diabetes, as a child's metabolism can rapidly deteriorate. A diabetes team experienced in working with children should be consulted as soon as possible [Bangstad et al. 2007].

### 4.2 Therapeutic objectives

Initial treatment and long-term care should be carried out continuously from the 1st year through to the 18th year of age – and in certain cases until the 21st year – by a diabetes team experienced in working with children. The specialized care is proven to contribute to a decrease in time spent in the hospital and hospital readmissions, a lower HbA1c value with 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 a care team should include:

- insulin therapy
- individual self-monitoring of metabolism
- structured learning program according to age
- psychosocial care for the affected families

The following medical aims are at the forefront of care for pediatric patients with diabetes mellitus [Danne et al. 2014]: avoidance of acute metabolicdecompensation, prevention of microvascular and macrovascular complications related to diabetes, and normal physical development (growth, weight gain, onset of puberty). The psychosocial development of patients should be impaired as little as possible by diabetes and its treatment, while integration and inclusion in kindergarten, grade school, and vocational training should be ensured.

Individual therapy objectives should be formulated with the child or adolescent and his/her family (HbA1c value, target blood glucose range, changes in behavior in the event of risk-prone lifestyles, efforts to integrate, etc.).

The targeted HbA1c value should be < 7.5 %, without hypoglycemia occurring. Fluctuations in blood glucose should be kept as minimal as possible [Bangstad et al. 2007; Clarke et al. 2008a]. Recommended values for blood glucose are given in ▶ **Table. 1** according to [Rewers et al. 2007].

▶ **Table. 1** Recommended orientation values for blood glucose monitoring[1].

| Blood glucose (BG) monitoring: clinical-chemical evaluation | healthy | good | moderate (measures recommended) | poor (measures required) |
|---|---|---|---|---|
| preprandial or fasting BG (mmol/l or mg/dl) | 3.6–5.6<br>65–100 | 5–82<br>90–145 | >8<br>>145 | >9<br>>162 |
| Postprandial BG (mmol/l or mg/dl) | 4.5–7.0<br>80–126 | 5–10<br>90–180 | 10–14<br>180–250 | >14<br>>250 |
| Nightly BG[3] (mmol/l or mg/dl) | 3.6–5.6<br>65–100 | 4.5–9<br>80–162 | <4.2 or >9<br><75 or >162 | <4.0 or >11<70<br>or >200 |
| HbA1c value (%) (standardized measurement acc. to DCC trial guidelines) | <6.05 | <7.5 | 7.5–9.0 | >9.0 |

[1] These general orientation values have to be adapted to the individual circumstances of a given patient. Deviating values are especially typical for small children, patients with severe hypoglycemia, or patients that are not capable of recognizing hypoglycemia [Cranston et al. 1994]; [2] If fasting blood glucose is under 72 mg/dl (under 4 mmol/l), the possibility of hypoglycemia having occurred previously at night should be considered [Holl et al. 1992]; [3] These figures are based on clinical studies, however, there are no strict, evidence-based recommendations.

The average frequency of blood glucose testing should be between 5 and 6 times a day; however, it may be considerably higher in particular cases [Ziegler et al. 2011].

## 4.3 Continuous treatment of type 1 diabetes

In order to ensure a metabolism that is as close to normoglycemic levels as possible as well as unimpeded psychosocial development, the continuity of treatment for diabetes mellitus is a decisive factor over the course of time and with regard to the different life and development phases of a child and adolescent with diabetes.

### Care for children in kindergartens and schools

Children with diabetes should receive care in mainstream kindergartens/elementary schools [Hellems and Clarke 2007].

An individual plan should be created for the institution (e. g., kindergarten, school, after-school care) in terms of the frequency and intervention limits of blood sugar/glucose measurement, insulin administration (mode, time, dosage calculation), defined mealtimes, symptoms, and management of hypoglycemia and hyperglycemia [American Diabetes Association (ADA) (2015)].

### Care during transition into young adulthood

The transition period from pediatric to adult diabetic care applies to young people with diabetes aged from 16 to 21 years in a life period characterized by general radical changes and requires special support (transition counseling, structured transition) [Nakhla et al. 2008; Australasian Paediatric Endocrine Group et al. 2005a; Court et al., (2008)].

### Care in the event of illness and avoidance of associated risks

In case of severe illness and perioperatively, diabetic children should be referred to a center with appropriate experience and proper resources. The pediatric diabetologist should be involved [Brink et al. 2007].

Under no circumstances insulin should be forgone in the event of low glucose levels or when food is being refused. Intake of carbohydrates is necessary to avoid substrate deficiency and ketone body development.

Children with diabetes mellitus should be vaccinated according to STIKO recommendations.

### Diabetes treatment with regard to physical activity/sports

Regular athletic activities improve metabolic control. Regular swimming is proven to significantly decrease the HbA1c value [Sideravicite et al. 2006].

Because blood sugar levels drop as a result of energy consumption during sports, the risk of hypoglycemia rises. The strongest predictor of hypoglycemia is the initial glucose value, which should be at least 120 mg/dl (6.6 mmol/l) [Tansey et al. 2006].

## 4.4 Insulin treatment

The standard treatment for pediatric patients affected by type 1 diabetes should be intensified insulin therapy.

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

The 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].

For pediatric patients, human insulin or insulin analogues should be used [Bangstad et al. 2007; Danne et al. 2005; Mortensen et al. [2000; Deeb et al. 2001; Plank et al. 2005; Simpson et al. 2007].

For intravenous insulin treatment, normal insulin should be employed.

### Short-acting insulins and insulin analogues (prandial substitution)

Short-acting human insulin and fast-acting insulin analogues display different results in children regarding onset and duration of effect, and can be used flexibly for prandial substitution in children depending on the situation [Danne et al. 2005; Mortensen et al. 2000].

For insulin pump therapy, short-acting insulin analogues should be used.

### Long-acting insulins and insulin analogues (basal substitution)

Both NPH insulin and long-acting insulin analogues can serve individually as a basal insulin substitution for 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

For the following indications, an insulin pump therapy should be considered:

- small children, particularly newborns, infants and pre-school children,
- children and adolescents with a notable rise in blood sugar in the early hours of the morning (dawn phenomenon),
- severe hypoglycemia, recurring and night-time hypoglycemia (despite intensified conventional therapy = ICT),
- HbA1c value outside of the target range (despite ICT),
- beginning microvascular or macrovascular complications,
- restricted quality of life through insulin treatment so far,
- children with excessive fear of needles,
- pregnant adolescents (in the event of planned pregnancy, ideally preconceptionally),
- competitive athletes,
- significant fluctuations in blood sugar irrespective of HbA1c value (despite ICT)

[Phillip et al. 2007].

Continuous glucose measurement (CGM), sensor-assisted insulin therapy, and sensor-assisted insulin pump therapy

CGM systems can be used with ICT (sensor-assisted insulin therapy]). 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 designated as sensor-assisted insulin pump therapy. Furthermore, there is the possibility of stopping the basal rate if the tissue glucose reaches a critical limit (sensor-assisted insulin pump therapy + low-glucose suspend [LGS]).

CGM should be employed in children and adolescents with type 1 diabetes and insulin pump therapy

- to decrease the rate of hypoglycemia (frequency, duration, depth) or
- in case of recurring nightly hypoglycemia or
- in case of lack of perception of hypoglycemia or
- in case of severe hypoglycemia having taken place

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

CGM should be considered and, if applicable, employed in pediatric patients with type 1 diabetes if the HbA1c target value is not reached after the exhaustion of other metabolism-optimizing and educational measures [Battelino et al. 2012; Bergenstal et al. 2010].

## 4.5 Dietary recommendations

The dietary advice included in patient education is an important part of the comprehensive therapy plan. The dietary advice for children and adolescents with diabetes should cover the following components:

- explanation of the impact that carbohydrates, fats, and proteins have on one's blood sugar,
- reinforcement of healthy diets within the family and in public institutions: regular, balanced mealtimes with snacks in between (fruit, vegetables, raw food), prevention of eating disorders (particularly binge-eating, i. e. uncontrolled hunger attacks), and prevention of overweight,
- sufficient energy for age-related growth and age-appropriate development,
- aiming for a normal BMI, which includes regular bodily activity,
- balance between energy intake and
- consumption in accordance with the insulin activity profiles,
- diet in the event of illness and sports,
- reduction of risk of cardiovascular diseases,
- consideration of cultural eating habits.

modified according to [Smart et al. 2014]).

The dietary advice should be given by dietary specialists (diet assistants/ecotrophologists) with in-depth knowledge of children's and adolescents' diets and insulin treatment [Smart et al. 2014; Craig et al. 2011].

Dietary recommendations should include all dietary components and the proportion they make up of one's daily energy intake [Deutsche Gesellschaft für Ernährung DGE et al, Österreichische Gesellschaft für Ernährung ÖGE, Schweizerische Gesellschaft für Ernährungsforschung SGE(2015].

## 4.6 Diabetes education

The patient education is an integral component of the therapy. Without appropriately coordinated medical treatment, it is not successful [Bloomgarden et al., (1987); deWeerdt et al., (1991)].

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

Supervisors in institutions (e. g., teaching staff at school and caretakers in kindergartens, child care facilities, nurseries, or group homes) should be offered educational sessions [Hellems and Clarke 2007; Lange et al. 2012; Clarke et al. 2013].

The educational sessions should be carried out by an interdisciplinary diabetes team with sufficient knowledge of the age-specific needs, opportunities and requirements of current diabetes treatments for patients and their families.

The educational component should be conducted by all team members, and jointly formulated treatment concepts and aims should ensue [Swift et al. 2010; Lange et al. 2014a; Cameron et al. 2013].

The learning process should be accompanied by evaluated educational documents that are oriented toward the cognitive development and needs of children and adolescents. The same applies to the educational materials for parents, including the childrearing tasks and age-specific diabetes treatment of their children [Martin et al. 2012; Lange et al. 2012; Lange et al. 2014a].

Diabetes education is a continuous process that is successful only through repeated, need-based offers (at least once every 2 years) during long-term care. New treatment concepts, for example initiation of insulin pump treatment or continuous glucose measurement (CGM), and new stages of life (e. g., starting school) should be accompanied with extra educational sessions. Further conditions (e. g., celiac disease or ADHD) or acute complications (e. g., DKA, severe hypoglycemia) or mental health problems re-

quire personalized schooling [Jacobson et al. 1997; Haas et al. 2014; Lange et al. 2014b; Delamater et al. 2014].

### 4.7 Rehabilitation

Inpatient rehabilitation can be carried out

- if a patient's ability to handle their diabetes proves deficient over a longer period
- in the event of secondary diseases related to diabetes or current threat of such diseases,
- after stationary primary treatment of newly diagnosed diabetes mellitus, in the event that no initial schooling can be carried out due to lack of nearby options (follow-on care),
- in the event of long-term, insufficient metabolic control under outpatient care conditions, e. g., recurring hypoglycemia or ketoacidosis,
- in case of considerable negative impact on age-appropriate scope of activities and participation in day-to-day life, e. g., missing many days of school due to illness

(§ 4 SGB 9; Bundesarbeitsgemeinschaft für Rehabilitation)

[Bundesarbeitsgemeinschaft für Rehabilitation BAR (2008); Fröhlich et al. 2008; Deutsche Gesellschaft für pädiatrische Rehabilitation und Prävention, 2007; Stachow et al. 2001].

## 5 Psychological and Social Risks, Comorbidities and Interventions

When diabetes is diagnosed, the psychosocial situation of the family should be recorded as part of medical history. The families should receive psychosocial counseling. An interdisciplinary team should offer their therapeutic aid to tackle diabetes in accordance with the patient's needs. The mental health situation of the parents and other caregivers should be taken into account [Hürter 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, if applicable, stressful life events should be continuously recorded during long-term care (intellectual, academic, emotional, and social development) and should be considered during therapy.

Therefore, social workers and psychologists with diabetes-specific expertise should constitute a fixed component in an interdisciplinary diabetes team [Silverstein et al. 2005; Craig et al. 2011; de Wit et al. 2008; Delamater et al. 2014; Kulzer et al. 2013a; Kulzer et al. 2013b; Hilliard et al. 2011; Haas et al. 2014; de Wit et al., 2012].

Particularly with adolescents, signs of eating disorders or affective disorders (e. g., anxiety, depression, adjustment disorders) should be noted and, if applicable a specialist diagnosis should be carried out and early intervention undertaken.

In the event of a psychiatrically relevant disorder, child and youth psychiatrists or psychological psychotherapists should be involved, in order to initiate co-treatment as necessary. A treatment coordinated between a psychiatrist and a diabetes team should be aimed for [Northam et al. 2005; Lawrence et al. 2006; Delamater et al. 2014; Kulzer et al. 2013a; Kulzer et al. 2013b; Young et al. 2013].

Children and adolescents with diabetes display an increased risk of developing information-processing and learning disorders. Those especially affected are children with early-onset diabetes, severe hypoglycemia, and chronic hyperglycemia at an early age.

Therefore, the academic performance of children with an increased risk (diabetes diagnosis at under age 5, severe hypoglycemia / chronic hyperglycemia) should be recorded. With regard to learning difficulties, they, as all children, should be neurophysiologically and psychologically examined in order to clarify cases of learning disabilities and, if necessary, offer support [Delamater et al. 2014].

## 6 Acute Complications

### 6.1 Diabetic ketoacidosis

Diabetic ketoacidosis is a potentially life-threatening disease. It should be immediately treated in a specialized facility by an experienced pediatric diabetes team. A written treatment plan should be available for the treatment of 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 the following:

- pH < 7.3,
- bicarbonate < 15 mmol/l,
- hyperglycemia > 11 mmol/l, > 200 mg/dl,
- ketonuria and ketone detection in the serum.

There are three degrees of severity of ketoacidosis:

- mild (pH < 7.3; bicarbonate < 15 mmol/l),
- moderate (pH < 7.2; bicarbonate < 10 mmol/l),
- severe (pH < 7.1; bicarbonate < 5 mmol/l)

[Wolfsdorf et al. 2007].

The following treatment aims should be targeted in the event of ketoacidosis:

- circulatory stabilization with initial volume bolus with isotonic solution,
- then slow balancing-out of fluids and electrolytes,
- gradual normalization of blood sugar,
- balancing-out of acidosis and ketosis,
- avoidance of therapy complications (cerebral edema, hypokaliemia),
- diagnosis and treatment of triggering factors

[Australasian Paediatric Endocrine Group et al. 2005b; Wolfsdorf et al. 2014] (▶ **Table. 2**).

During treatment of severe diabetic ketoacidosis, clinical observation and monitoring should be carried out at least hourly [Australasian Paediatric Endocrine Group et al. 2005a; Edge et al., 2006; Wolfsdorf et al. 2014].

Pediatric patients with severe ketoacidosis and elevated risk of cerebral edema should be immediately treated by an experienced pediatric diabetes team in an intensive care unit or in a specialized diabetes ward with comparable equipment.

Patients with suspected cerebral edema should be treated in an intensive care unit in cooperation with an experienced diabetic

▶ **Table. 2** Pharmaceutical treatment of ketoacidosis (taking into consideration the monitoring of electrolytes, pH, blood sugar, ketone bodies).

| Objective of treatment / Indication | Medicinal product | Dose | Timespan) |
|---|---|---|---|
| Initial stabilization of circulation (if necessary | NaCl 0.9 % | 10–20 ml/kg i. v. | Immediately over 1–2 h |
| Balancing-out of fluids after initial stabilization of circulation | NaCl 0.9 % or Ringer's solution after 4–6 h, also NaCl 0.45 % possible | Maximal i. v. daily dose < 1.5 to 2x maintenance requirements for age/weight/body surface | At least over 36–48 h |
| Lowering of blood glucose | Normal insulin | 0.1U/kg/h i. v. with younger child 0.05U/kg/h | Start of insulin administration 1–2 h after start of volume administration; no interruption of insulin intake until pH > 7.3; blood sugar decrease by 2–5 mmol/l/h (36–90 mg/dl/h) |
| Avoidance of hypoglycemia | Glucose | Final concentration: 5 % glucose / 0.45 % NaCl solution | Start from blood glucose of 15 mmol/l (270 mg/dl) or with decrease in blood glucose > 5 mmol/l/h (90 mg/dl/h) |
| Potassium balancing | KCl | 40 mmol/l volume; 5 mmol/kg/day i. v.; not > 0.05 mmol/kg/h | With hypokalemia immediately, with normokalemia at start of insulin administration, with hyperkalemia only after re-initiation of urine production; continuous administration until completion of volume balancing |

team [Australasian Paediatric Endocrine Group et al. 2005b; Wolfsdorf et al. 2014].

Patients with significant signs of cerebral edema should be treated immediately with mannitol or hypertonic saline solution prior to the initiation of further diagnostic measures (MRI) [Australasian Paediatric Endocrine Group et al. 2005a; Fiordalisi et al. 2007; Hanas et al. 2007; Roberts et al. 2001; Franklin et al. 1982; Banks and Furyk 2008; Wolfsdorf et al. 2014].

Regarding the therapeutic effectiveness of early, possibly repeated (after 30 min.) intravenous administration of mannitol (0.5–1 g/kg) over 10–15 min in the event of symptomatic cerebral edema, case reports and case series are available in the literature [Fiordalisi et al. 2007; Hanas et al. 2007; Roberts et al. 2001; Franklin et al. 1982].

### 6.2 Hypoglycemia

Hypoglycemic episodes are the most common acute complications in diabetes [Diabetes Control and Complications Trial Research Group 1994].

They are classified as either

- mild hypoglycemic episodes, which are easily relieved by the patient by consuming fast-acting carbohydrates or
- severe hypoglycemic episodes, which can be remedied only through help from another person due to limited or loss of consciousness. In addition to unconsciousness, severe hypoglycemic episodes may cause seizures.

Children and adolescents with type 1 diabetes should always carry fast-acting carbohydrates with them in the form of glucose or similar substances so that they can act quickly in the event of a mild hypoglycemic episode in order to prevent severe hypoglycemic episodes. Parents or other primary caregivers should be trained in the administration of glucagon injections and other immediate measures.

Caregivers, for instance in preschools and child care facilities, as well as teachers in schools should also receive instruction on the risks and treatment options for hypoglycemia.

In case of hypoglycemia unawareness, a higher blood glucose level should temporarily be aimed for [Australasian Paediatric Endocrine Group et al. 2005a; Clarke et al. 2008a].

## 7 Long-term Complications and Screening

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

## 8 Associated Autoimmune Diseases

### 8.1 Diagnosis and treatment of thyroid diseases

In children and adolescents affected by diabetes, the levels of TSH and thyroid autoantibodies (anti-TPO, anti-Tg) should be determined upon diabetes onset, as well as regularly at annual or biennial intervals, or in the event of relevant symptoms [Australasian Paediatric Endocrine Group et al. 2005a; Bangstad et al. 2007; Silverstein et al. 2005; Kordonouri et al. 2011].

If TPO autoantibodies are present and/or a TSH increase is observed, an ultrasound of the thyroid should be carried out.

For treatment of autoimmune hypothyroidism or goiter, L-thyroxine should be employed acc. to the therapy plan (▶ **Fig. 1**).

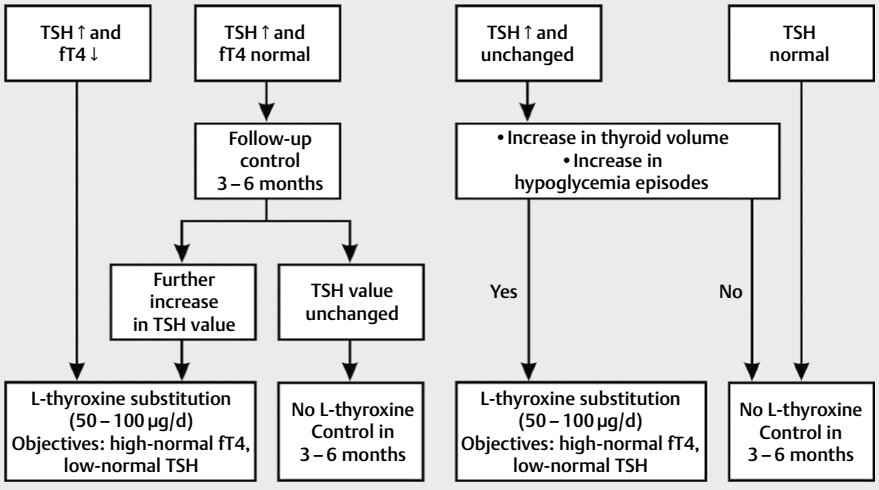
### 8.2 Diagnosis and treatment of celiac disease

Children and adolescents affected by diabetes should be examined for a potential celiac disease diagnosis upon diabetes onset, as well as regularly at annual or biennial intervals, or in the event of relevant symptoms [Australasian Paediatric Endocrine Group et al. 2005a; Hill et al. 2005; Silverstein et al. 2005; Kordonouri et al. 2007; Kordonouri et al. 2014; Kordonouri et al. 2011].

In case of (serologically and bioptically) confirmed celiac disease with symptoms or extra-intestinal manifestations, a gluten-free

▶ **Table. 3** Long-term complications: screening examinations and interventions.

| Screening examination and intervals | Recommended screening method(s) | Interventions |
|---|---|---|
| 1. Retinopathy:<br>– every 1–2 years;<br>– from the age of 11 years or as of 5 years of diabetes | binocular bimicroscopic ophthalmoscopy in mydriasis by experienced ophthalmologist | – improvement of glycemic control<br>– normalize blood pressure<br>– normalize dyslipidemia<br>– laser therapy<br>– intravitreal injections |
| 2. Nephropathy:<br>– every year;<br>– from the age of 11 years or as of 5 years of diabetes | evidence of microalbuminuria:<br>– concentration measurement: 20–200 mg/l<br>– albumin excretion rate > 20- < 200 µg/min<br>– albumin-creatinine ratio | – improvement of glycemic control<br>– in case of hypertension + microalbuminuria:<br>– ACE inhibitor<br>– AT1 blocker<br>– persisting microalbuminuria without hypertension: consider ACE inhibitor<br>– nicotine abstinence |
| 3. Neuropathy:<br>– yearly from the age of 11 or as of 5 years of diabetes in the event of long-term poor metabolic status | – medical history<br>– pressure sensation (monofilament)<br>– vibration perception (tuning fork test)<br>– proprioceptive reflexes | – improvement of glycemic control |
| 4. Hypertension:<br>– every 3 months, at least once a year, from the age of 11 | – RR (resting)<br>– 24 h RR at least twice > 95th percentile or microalbuminuria | – lifestyle intervention (physical activity, salt restriction, weight reduction, reduction of alcohol, nicotine)<br>– if not successful: ACE inhibitor; in the event of contraindication or adverse effects: AT1-blocker; if required, combination with other medicines |
| 5. Hyperlipidemia<br>– within 1 year of diagnosis<br>– then every 2 years<br>– prepubertal every 5 years | determination of<br>– total cholesterol<br>– HDL<br>– LDL<br>– triglycerides | – dietary therapy<br>– if not successful: statins from the age of 8 years |




▶ **Fig. 1 Treatment plan for Hashimoto's thyroiditis [rerif].**

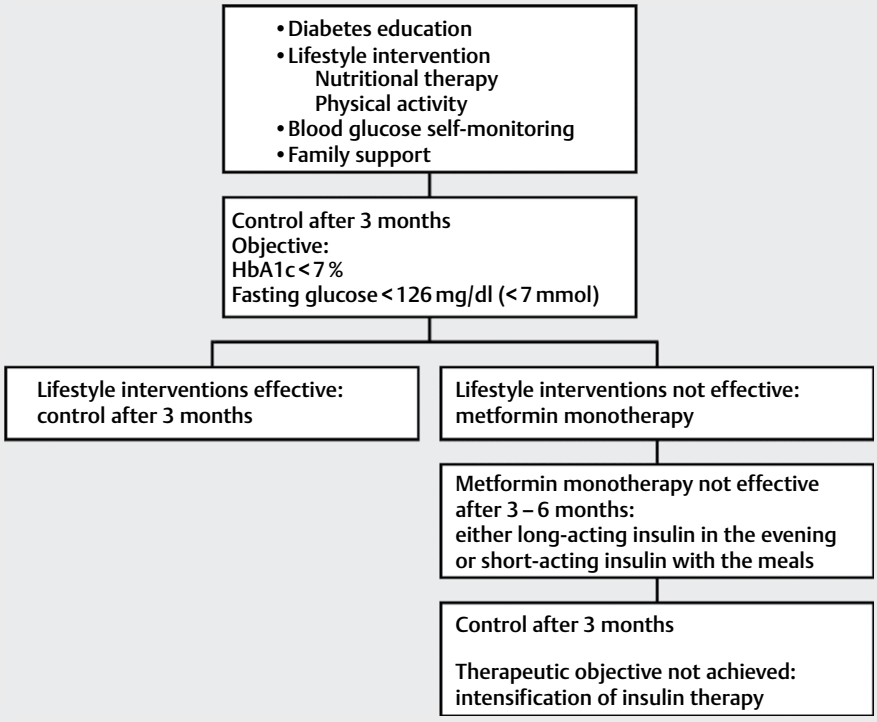
diet should be introduced [Hansen et al. 2006; Amin et al. 2002; Hill et al. 2005; Lewis et al. 1996; Kordonouri et al. 2011].

In asymptomatic patients, the indication for gluten-free diet and further follow-up should be discussed with the pediatric gastroenterologist.

# 9 Other Forms of Diabetes in Childhood and Adolescence

## 9.1 Type 2 diabetes

Type 2 diabetes in adolescents should be diagnosed based on the limit values for fasting blood glucose and an oral glucose tolerance test (OGTT) in compliance with the standard or reference method.




▶ **Fig. 2 Treatment plan for type 2 diabetes in children and adolescents [rerif].**

If the following limit values are exceeded, the result of an asymptomatic patient should be confirmed via a second test on another day:
- fasting blood sugar: > 126 mg/dl ( > 7.0 mmol/l)
- OGTT: 2 h value > 200 mg/dl ( > 11.1 mmol/l)

[Genuth et al. 2003].

Additional laboratory tests may be of help for differentiating between type 2 and type 1 diabetes:
- C-peptide
- diabetes-specific autoantibodies (GAD, iA2, ICA, IAA) [Alberti et al. 2004; Genuth et al. 2003].

For the treatment of type 2 diabetes in adolescents, a fasting blood glucose level of < 126 mg/dl and an HbA1c value of < 7 % should be aimed for [Zeitler et al. 2014; UK Prospective Diabetes Study UKPDS Group (1998b); Holman et al. 2008]. A detailled treatment plan according to [Alberti et al. 2004] is given in Figure 2 (▶ **Fig. 2**).

The schooling for adolescents with type 2 diabetes should include dietary advice and guidance on physical activity within the framework of a structured obesity program [Reinehr et al., 2007; Arbeitsgemeinschaft Adipositas im Kindes- und Jugendalter (AGA): Therapie der Adipositas im Kindes- und Jugendalter (2008)].

Moreover, the content relevant to type 2 diabetes should be carried over from the type 1 diabetes schooling on an individually adjusted, modular basis.

In the event of an initial HbA1c value of ≥ 9 % or spontaneous hyperglycemia of ≥ 250 mg/dl and in case of signs of absolute insulin deficiency (ketonuria, ketoacidosis), an initial insulin treatment should be started. In all other cases, metformin is the first-line drug for the pharmaceutical treatment of children and adolescents [Shimazaki et al. 2007; UK Prospective Diabetes Study UKPDS Group (1998a); Jones et al. 2002; Jones et al. 2002; Gottschalk et al. 2007; Zeitler et al. 2014].

## 9.2 Monogenic diabetes

Due to the significance for therapy, long-term prognosis and genetic counseling of families, molecular genetic diagnostics of the MODY forms (▶ **Table. 4**) are recommended in the event of substantiated suspicion of these. The most common forms are listed according to [Hattersley et al. 2006; Ellard et al. 2008] in Table 4.

Before the affected genes are sequenced, counseling and information must be provided pursuant to the German Gene Diagnostics Law (Gendiagnostikgesetz), particularly with regard to the right to know and the right not to know about genetic information [Murphy et al. 2008; McDonald et al. 2013; Ellard et al. 2008; [Badenhoop et al. 2008]; Gene diagnostics law 2009].

## 9.3 Neonatal diabetes mellitus (NDM)

One particular form of genetic diabetes is neonatal diabetes mellitus (NDM), which develops within the first 6 months of life. From a clinical perspective, two subgroups are distinguished, namely transient (TNDM) and permanent (PNDM) neonatal diabetes mellitus. Regarding the diagnosis of neonatal diabetes or manifestation of diabetes within the course of 6 months of life, see (▶ **Table. 5**).

In the event of etiologically undetermined neonatal diabetes mellitus and diabetes mellitus which occurs within the first 6 months of life, a molecular-genetic analysis should be carried out as early on as possible in order to initiate appropriate therapy as

▶ **Table. 4** The most common MODY forms and their clinical characteristics.

| MODY type (international proportion in percent); heredity | Age (in years) at manifestation | Severity of hyperglycemia | Clinical presentation |
|---|---|---|---|
| HNF1A-MODY (MODY3) HNF-1α- (20–50 %) autosomal-dominant | 14 (4–18) | severely hyperglycemic | – significant rise in blood glucose level in the OGTT (> 90 mg/dl), low renal threshold (frequent glycosuria associated with blood glucose levels < 180 mg/dl [< 10 mmol/l]),<br>– increasing hyperglycemia with age,<br>– response to sulfonylurea/glinides |
| GCK-MODY (MODY2) glucokinase (20–50 %) autosomal-dominant | 10 (0–18) | mildly hyperglycemic | – often discovered incidentally,<br>– fasting blood glucose level slightly elevated between 99 and 144 mg/dl, (5.5–8 mmol/l),<br>– small blood glucose increase in the OGTT (by < 63 mg/dl or < 3.5 mmol/l),<br>– no blood glucose deterioration with age,<br>– rarely any microvascular or macrovascular complications, even without pharmaceutical treatment |
| HNF4A-MODY (MODY1) HNF-4α- (1–5 %) autosomal-dominant | 17 (5–18) | significantly hyperglycemic | – similar to HNF-1α, but renal threshold normal,<br>– response to sulfonylurea |

▶ **Table. 5** Neonatal diabetes – diagnostic procedure.

| Diagnostic procedure in case of diabetes manifestation up to 6th month of life, if necessary up to 1st year |
|---|
| 1.Ruling out pancreatic insufficiency<br>– ultrasound to rule out pancreatic aplasia<br>– analysis of fecal elastase to rule out exocrine insufficiency |
| 2.If ultrasound is normal or inconclusive:<br>– testing of diabetes-specific autoantibodies (GAD, IA2, ICA, IAA) |
| 3.If ultrasound is normal or inconclusive, autoantibodies negative and fecal elastase normal: molecular genetic analyses for a differential diagnosis of:<br>– anomalies of 6q24 chromosome (TNDM),<br>– mutations of KCNJ11 gene (PNDM, TNDM),<br>– mutations of ABCC8 gene (PNDM, TNDM),<br>– mutation of insulin gene (PNDM). |
| 4.In case of decreased fecal elastase and negative molecular genetic analysis regarding chromosome 6q24, KCNJ11, ABCC8, and insulin gene as well as negative or positive autoantibodies:<br>– examination for less common genetic diseases/genetic syndrome |

soon as possible in case of sulfonylurea-sensitive mutations [Flanagan et al. 2006; Babenko et al. 2006; Klupa et al. 2008; Battaglia et al. 2012; Shah et al. 2012].

Initially, insulin therapy should always be carried out in case of neonatal diabetes. If a KCNJ11 or ABCC8 gene mutation is present, treatment with sulfonylurea should be attempted as early as possible [Hattersley et al. 2006; Pearson et al. 2006 I; Mlynarski et al. 2007; Koster et al. 2008; Slingerland et al. 2008; Thurber et al., (2015)].

### 9.4 Cystic fibrosis-related diabetes

Since cystic fibrosis-related diabetes (CFRD) is often difficult to clinically diagnose, children with cystic fibrosis should undergo an annual glucose tolerance test after 10 years of age [Lanng et al. 1994].

In case of a confirmed diabetes diagnosis, treatment of CFRD should be initiated [Nousia-Arvanitakis et al. 2001; Rolon et al. 2001; Lanng et al. 1994; Dobson et al. 2002].

For long-term therapy of CFRD, insulin should be used. In the first 12 months after diagnosis, therapy can, however, be attempted with glinides or sulfonylurea [Ballmann et al. 2014; O'Riordan et al. 2008].

In the event of cystic fibrosis, a diet high in fat and calories should be adhered to even after diabetes diagnosis. Reduction of calories is contraindicated [O'Riordan et al. 2008].

## Imprint

The evidence-based guidelines were prepared on behalf of the German Diabetes Society (DDG). The German Diabetes Society is represented by the president responsible (2015–2017 Prof. Dr. B. Gallwitz) and the guidelines project manager of the DDG (Prof. Dr. Monika Kellerer).

The guidelines group comprises members of the German Pediatric Diabetology Association (AGPD), members of the 2009 guidelines group as well as a patient representative.

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### Conflicts of Interest

The conflicts of interest of all members of the guidelines group are detailed exhaustively in the long version of the guidelines (Table 32).

# Supplementary Material

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