Diagnosis, Therapy and Control of Diabetes Mellitus in Children and Adolescents

Authors A. Neu[1], P. Beyer[2], J. Bürger-Büsing[3], T. Danne[4], J. Etspüler[5], B. Heidtmann[6], R. W. Holl[7], B. Karges[8], W. Kiess[9], I. Knerr[10], O. Kordonouri[4], K. Lange[11], R. Lepler[12], W. Marg[13], A. Näke[14], M. Petersen[15], A. Podeswik[16], R. Stachow[17], S. von Sengbusch[15], V. Wagner[15], R. Ziegler[18], P. M. Holterhus[19]

Affiliations Affiliation addresses are listed at the end of the article.

Concerns and Background

The following recommendations are directed to all professional and vocational groups which take care of and support children and adolescents with diabetes, as well as their families. It is also directed to higher level organisations, such as health insurers, which deal with diabetes. This guideline concentrates on the specifics for this age group which are not described in the DDG's general guidelines for the therapy of type 1 diabetes, or are described there, but somewhat differently [1]. As stated in the specifications of the health ministries of Germany's states and in keeping with the current practice of many clinics, this paediatric guideline applies to all diabetes patients who are not yet 18 years of age. In individual clinical cases this guideline can also be used for young adults.

Epidemiology and Forms of Diabetes in Childhood and Adolescence

Type 1 Diabetes

Type 1 diabetes is the most frequent metabolic disease in childhood. According to the latest estimates, there are some 10 000 to 15 000 children aged 14 years or under who live in Germany and have type 1 diabetes [2–4]. For persons in Germany aged 19 years or under this figure is 21 000 to 24 000 [3].

These figures are rising at a rate of 3 to 5 % per year [4–6]. The number of new cases per year of type 1 diabetes diagnosed among children aged 14 years or under is now twice what it was in the early 1990 s. This rate was at 20.9 % in 2001 (95 % confidence interval of 18.7–23.2). Most of the rise is in the younger age groups.

Type 2 Diabetes

The frequency of type 2 diabetes in this age group has increased in parallel to the rise of overweight and obesity in children and adolescents [7, 8]. Initial population based estimates of type 2 diabetes in children and adolescents in 2002 indicate an incidence of 1.57 per 100 000 inhabitants (95 % confidence interval of 0.98–2.42) [9]. Research in Baden-Württemberg from the year 2004 shows that type 2 diabetes occurs with an incidence of 2.3 per 100 000 inhabitants among 0 to 20-year-olds in Germany [10].

Risk Factors, Prevention and Early Recognition

Type 1 Diabetes

General screening for type 1 diabetes should not be conducted among children and adolescents in the general public or in high risk groups (B) [11]. The risk of developing diabetes is three times as high for a child whose father has diabetes than it is for a child whose mother has diabetes [12]. While antibodies and other markers do allow a prediction and risk calculation that a given person will develop diabetes, there are no effective strategies that could prevent manifestation of diabetes. [13, 14].

Type 2 Diabetes

An oral glucose tolerance test for early recognition of type 2 diabetes should be conducted for all overweight children (BMI > percentile 90) of age 10 or older who have two or more of the following risk factors (A) [15].

- A close blood relation has type 2 diabetes
- Membership of a group with elevated risk (e. g. East Asians, Afro-Americans, Hispanics)
- Extreme obesity (BMI > Percentile 99.5)
- Signs of insulin resistance or of changes associated with it (arterial hypertension, dyslipidaemia, elevated transaminases, polycystic ovary syndrome, acanthosis nigricans).

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Bibliography
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Correspondence
Prof. Dr. med. Andreas Neu
Universitätsklinikum Tübingen, Klinik für Kinder- und Jugendmedizin
Hoppe-Seyler-Str. 1
72076 Tübingen
Tel.: 0 70 71/2 98 37 81
Andreas.Neu@med.uni-tuebingen.de

Therapy of Type 1 Diabetes

Beginning of Therapy

Insulin therapy should begin when the diagnosis of type 1 diabetes is made because a child's metabolism can deteriorate rapidly. A team experienced in treating diabetic children should be consulted as soon as possible [16].

Therapy Objectives

Initial treatment and continual care until the patient turns 18, or possibly 21 in individual cases, should be undertaken by a team experienced in treating diabetic children (A).

It has been shown that specialised care contributes to a reduction of days spent in hospital and admissions to hospital, and to lower HbA1c levels with better disease management and fewer complications [17].

Treatment of type 1 diabetes by the treatment team should comprise (B):

- Insulin therapy
- Age adapted structured education
- Psychosocial care of the family affected.

Individual therapy objectives should be formulated with the patient and his or her family (HbA1c level, blood sugar target ranges, behavioural changes in cases of risky life style, efforts by migrants to be integrated, etc.) (A).

Blood sugar level should be checked between 5 and 8 times a day, or even more frequently in some cases.

Continual Treatment of Type 1 Diabetes

Care of Children in Kindergartens and Schools

Children with diabetes should be cared for in general kindergartens and grade schools (A) [21]. An individual plan should be drawn up for the patient's educational facility in respect to frequency and intervention levels of the blood sugar measurements, administrations of insulin (mode, time, computation of dosage), times for meals, and symptoms and management of incidents of hypoglycaemia and hyperglycaemia (A) [22].

Care During Transition to Young Adult Age

The transition from paediatric to general medical care affects young diabetics aged 16 to 21 in a life phase of general upheavals and should be guided, for example by special consultation, structured transfer from the paediatrician to a specialist for adults (B) [23–25].

Care during illness and avoidance of health risks

When they are seriously ill or about to undergo surgery, children with diabetes should be referred to a centre that is experienced in and equipped for diabetes. The paediatric diabetologist should be called in (A) [26].

In no case may insulin be completely omitted because of low blood sugar levels or refusal of food. Rather, it is necessary to administer carbohydrates so that lack of substrate and formation of ketone bodies are avoided.

Children with diabetes mellitus should be vaccinated in accordance with the STIKO recommendations (B).

Insulin Treatment

The treatment standard for paediatric patients with type 1 diabetes should be that of intensified insulin therapy (B) [27–29].

Insulin therapy should be conducted in the context of comprehensive diabetes care which includes support of the patient's family (A).

Insulin therapy should be designed individually for each child (A).

Human insulin or insulin analogues should be used for paediatric patients (A) [31–36].

Intravenous insulin treatment should use regular insulin (B).

Short-Acting Insulins and Insulin Analogues (Prandial Substitution)

In the case of children, short-acting human insulin and insulin analogues display differences in respect to the beginning and duration of their action and, depending on the situation, can be used flexibly for children as prandial substitution [32, 33].

Insulin pump therapy should use short-acting insulin analogues (B).

Long-Acting Insulins and Insulin Analogues (Basal Substitution)

Both NPH-insulin and long-acting insulin analogues can be used individually for basal insulin substitution in children [37-40].

Insulin Pump Therapy

Insulin pump therapy should be considered when the following indications are present (B) (modified as in [41])

- Small children, especially newborns and pre-school children
- Children and adolescents with pronounced blood sugar rise in the early morning hours (dawn phenomenon)
- severe hypoglycaemia, recurring and nocturnal hypoglycaemia (despite intensified conventional therapy = ICT)

Table 1 Standard recommended values for blood glucose control [18].

Blood sugar control, clinical-chemical assessment[1]	Healthy subjects	Metabolism good	Metabolism fair (measures recommended)	Metabolism poor (measures required)
preprandial or fasting BG (mmol/L or mg/dL)	3.6–5.6 65–100	5–8[2] 90–145	>8 >145	>9 >162
postprandial BG	4.5–7.0 80–126	5–10 90–180	10–14 180–250	>14 >250
nocturnal BG[3]	3.6–5.6 65–100	4,5–9 80–162	<4.2 or >9 <75 or >162	<4.0 or >11 <70 or >200
HbA1c level (standardised measurement in % by specifications of the DCC trial)	<6.05	<7.5	7.5–9.0	>9.0

[1] These standard values must be adapted to the patient's individual circumstances. Other standard values apply particularly to small children, patients with severe hypoglycaemia and patients who are not in a position to recognize hypoglycaemia [17].

[2] If fasting blood glucose is under 72 mg/dL (4 mmol/L) in the morning, the possibility of preceding nocturnal hypoglycaemia should be considered [18].

[3] These figures are based on clinical studies, but no strict evidence based recommendations are available.

- HbA1c level outside the target range (despite ICT)
- Incipient micro or macrovascular secondary diseases
- Limited life quality due to previous insulin treatment
- Children with needle phobia
- Pregnant adolescents (preferably preconceptional if pregnancy planned)
- Athletes
- Large fluctuations in blood sugar that are independent of the HbA1c level (despite ICT).

Dietary Recommendations

Nutritional counselling in the context of diabetes education is an important part of any comprehensive therapy plan. Nutrition counselling for children and adolescents with diabetes should include the following points (A), as modified in accordance with [42]:

- Explanation of the effectiveness of carbohydrates, fats and proteins on blood sugar;
- Strengthening of healthy dietary habits in the family and in public facilities: regular balanced meals and snacks (fruit, vegetables, and uncooked vegetarian food), prevention of eating disorders such as binge eating, and prevention of overweight;
- Sufficient energy for age appropriate growth and development;
- Effort to reach and maintain normal BMI, both through diet and regular physical activity;
- Balance between energy intake and consumption in agreement with the type of insulin;
- Proper diet in case of illness;
- Proper diet for sports;
- Reduction of the risk of cardiovascular diseases;
- Due account of cultural dietary habits;

Dietary recommendations should cover all nutritional components and their portions in daily intake of energy (B) [43, 44].

Diabetes Education

Education for each patient is an integral part of diabetes therapy. Education can be successful only if it is coordinated with adequate medical treatment [45, 46].

The patients (children and adolescents) and their parents or other primary care givers should have continual access to qualified educational activities when diabetes is diagnosed (A) [47, 48].

Persons in authority relative to the patient such as teachers in kindergarten or grade school should be offered diabetes education (A) [21].

The educational sessions should be conducted by a multi-professional diabetes team which has sufficient knowledge of the age specific needs and options of the patients and of the requirements placed on the patients and their families (A).

The sessions should be conducted by all the members of the team and follow uniform, therapy concepts and objectives which they have formulated together (A) [47, 48].

Diabetes education is a continual process which can be successful only through offers that are repeated at least once every two years during long-term care. New therapy concepts (e.g. pump therapy) and new life phases (e.g. enrolment in grade school) should be accompanied by additional explanatory sessions (A) [48-50].

Rehabilitation

In-patient rehabilitation is an option (0) [51 – 56]:

- with persistent lack of skills in dealing with diabetes;
- with existent or currently impending secondary diseases;
- after stationary primary therapy of newly diagnosed diabetes mellitus if no initial education is available at a location near the patient's home
- with long-term insufficient metabolism control under out-patient conditions, for example with recurrent hypoglycaemia or ketoacidosis
- with significant disruption of activities and/or participation of the child/adolescent in an age appropriate daily routine.

Psychological and Social Risks, Comorbidities and Interventions

When children and adolescents are diagnosed with diabetes, their families should be advised psycho-socially and offered ther-

Table 2 Medical treatment of diabetic ketoacidosis.

Treatment objective/ Indication	Medication	Dose	Time period/sequence
initial stabilisation of circulation (if required)	NaCl 0.9 %	10 – 20 ml/kg i. v.	immediately, over 1 – 2 hours
administration of fluids after initial stabilisation of circulation	NaCl 0.9 % or Ringer's solution after 4 – 6 hours; NaCl 0.45 % also possible	at most i. v. daily dose < 1.5 to 2.0 times maintenance requirements in view of age, body weight and body surface.	at least over 36 – 48 hours
lower blood glucose	regular insulin	0.1 U/kg/h i. v. for fairly young child: 0.05U/kg/h	beginning of insulin administration 1-2 hours after beginning of volume administration; no interruption of insulin administration until pH > 7.3; reduction of blood sugar by 2-5 mmol/L/h (36-90 mg/dL/h)
avoidance of hypoglycaemia	glucose	final concentration: 5 % glucose/ 0.45 % NaCl solution	starting at blood sugar = 15 mmol/L (270 mg/dL) or with blood sugar reduction > 5 mmol/L/h (90 mg/ dL/h)
potassium balance	KCl	40 mmol/ L volume; 5 mmol/kg/day i. v.; not > 0.5 mmol/kg/h	immediately if hypokalemia: at start of insulin administration if normokalemia; not until urine production has resumed if hyperkalemia; continual administration until termination of volume administration

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

Screening examination and intervals	Recommended screening methods	Interventions
1. retinopathy: – every 1 – 2 years – from age 11 or – after 5 years of diabetes	binocular bimicroscopic funduscopy with dilated pupil, performed by an experienced eye doctor	– improvement of glycaemic control – laser therapy
2. nephropathy: – once a year – from age 11 or – after 5 years diabetes	proof of microalbuminuria: – concentration at 20 – 200 mg/L – albumin excretion rate over 20 but under 200 µg/ min – Albumin creatinine ratio	– improvement of glycaemic control – ACE inhibitors – AT-I blockers – abstinence from nicotine
3. neuropathy: – in case of long-term poor metabolism annually – from age 11 or after 5 years of diabetes	– history – touch sensation (monofilament) – vibration sensation (tuning fork test) – deep tendon reflexes	– improvement of glycaemic control
4. hypertension – every 3 months – at least annually from age 11	– BP at rest – 24 hour BP with at least 2 times above percentile 95 or microalbuminuria	– life style intervention (activity, salt restriction, weight reduction, reduction of alcohol/ nicotine – if unsuccessful: ACE inhibitor
5. hyperlipidaemia: – during first year after diagnosis – every 5 years before puberty – then every 2 years	determination of – total cholesterol – HDL – LDL – triglyceride	– dietetic therapy – if unsuccessful, statins if patient at least 8 years old

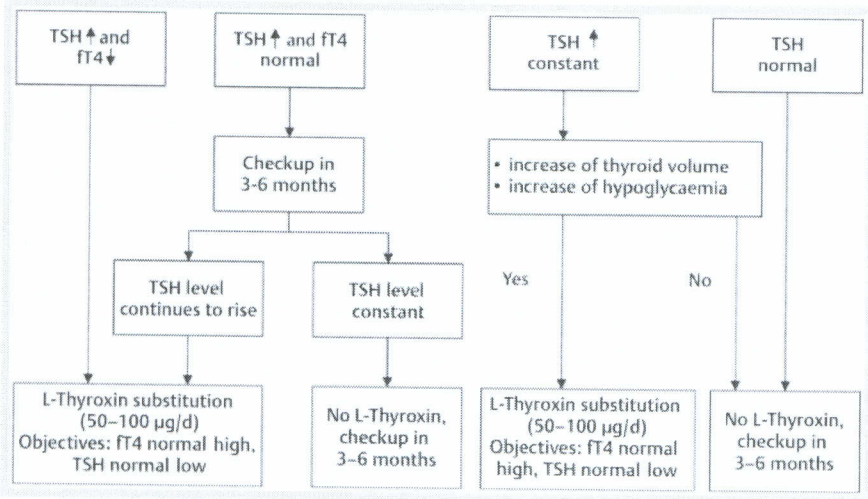

Fig. 1 Treatment of Hashimoto's Thyroiditis. The treatment depends on the TSH level.

apeutic assistance in facing diabetes. This should take account of the mental situation of the parents and other primary care givers (A) [24, 57 – 61].

Particularly in the case of adolescents, one should look for signs of eating disorders and affective disorders (anxieties, depression) and, as appropriate, have a proper diagnosis conducted and intervene early (A).

If there is a psychiatrically relevant disorder, an appropriate psychiatrist or psychologist should be called in to work with the diabetes team on a jointly agreed treatment plan (A) [24, 57, 62 – 71].

Acute Complications

Diabetic Ketoacidosis

The biochemical criteria for ketoacidosis comprise:

- pH < 7.3
- Bicarbonate < 15 mmol/L
- Hyperglycaemia > 11 mmol/L (200 mg/dL)
- Ketonuria and ketones detected in serum.

Diabetic ketoacidosis is a potentially life-threatening disease. It should be treated at once in a specialised facility by a diabetes team that is experienced in treating children. There should be a written plan for treating diabetic ketoacidosis in children and adolescents (A) [72-74].

The therapy objectives for ketoacidosis should be as follows (A):

- Stabilisation of circulation with initial bolus volume with isotonic solution, followed by
- Slow balancing of fluid and electrolyte balance,
- Slow normalisation of blood sugar,
- Equalisation of acidosis and ketones,
- Avoidance of therapy complications (cerebral edema, hypokalemia),
- Diagnosis and therapy of the factors responsible.

Treatment of severe diabetic ketoacidosis should include clinical observation and monitoring at least once an hour (A) [24, 75, 76].

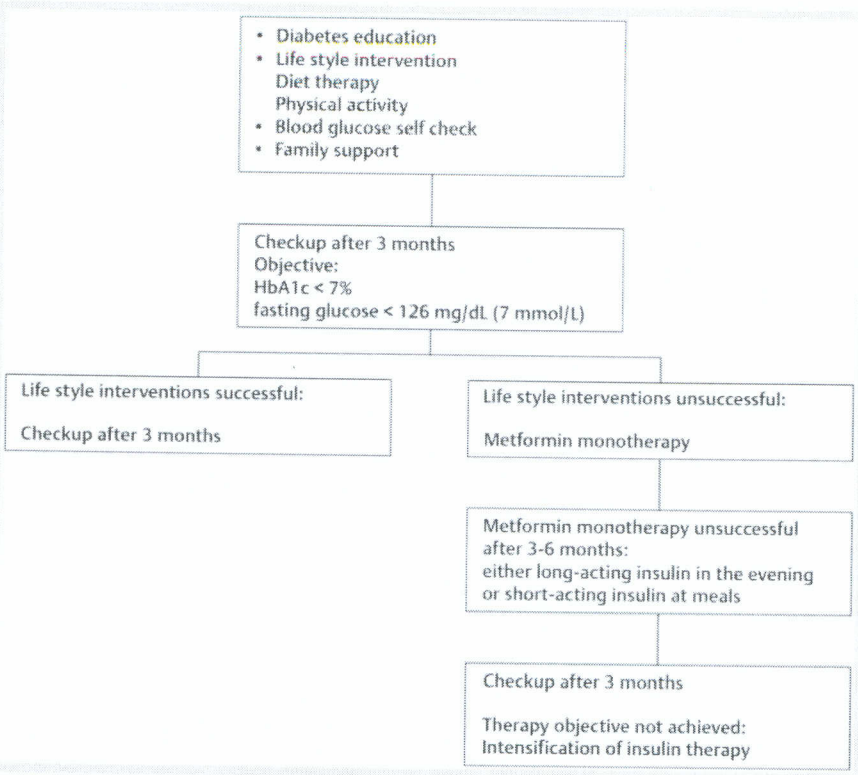

Fig. 2 Treatment of type 2 diabetes in children and adolescents [93].

Patients with severe diabetic ketoacidosis and increased risk of cerebral edema should be treated at once in an intensive care unit or specialised diabetes unit with comparable equipment by a diabetes team experienced in treating children (A) [11, 75].
Patients with clear signs of cerebral edema should be treated at once with mannitol i. v. (0.5-1 g/kg) for 20 minutes or 3 % hypertonic saline solution i. v. (5-10 ml/kg for 30 minutes to 2 hours) before other diagnostic measures (MRI) are taken. (A) [24, 74, 77 – 81].

Hypoglycaemia

Hypoglycaemia is the most frequent acute complication of diabetes.
Children and adolescents with type 1 diabetes should always carry with them short-acting carbohydrates in the form of dextrose or the like so that they are able to treat slight hypoglycaemia at once and thus prevent severe hypoglycaemia (A).
Parents and other primary care givers should be shown how to administer a glucagon injection and take other immediate action (A).
Care givers such as in nursery schools and kindergartens as well as teachers in schools should likewise receive instruction in the risks and treatment options for hypoglycaemia (B).
If the child or adolescent's ability to notice hypoglycaemia is impaired, then a higher blood sugar level should be aimed for temporarily. (A) [24, 82].

Long-Term Complications and Preventive Checkups

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The HbA1c level should be measured every three months as a check of metabolic control (A) [28, 29, 83].

Associated Autoimmune Diseases

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Diagnosis and Therapy of Thyroid Diseases

The thyroid stimulating hormone and thyroid autoantibody levels (TPO-AK, Tg-AK) should be determined in children and adolescents when they are diagnosed with diabetes and regularly at one to two year intervals thereafter of if any thyroid symptoms appear (A) [24, 84, 85].
If TPO autoantibodies and/or a TSH increase are detected, then a sonography of the thyroid should be taken (A).

Diagnosis and Therapy of Coeliac Disease

Children and adolescents should be examined for coeliac disease when they are first diagnosed with diabetes and regularly at one to two year intervals thereafter or if any symptoms thereof appear (A) [24, 86 – 88].
The patient should be put on a gluten-free diet if symptoms or extraintestinal manifestations of coeliac disease are present and serology and biopsy are positive. (A) [86, 89 – 91].
If the patient is asymptomatic, the decisions on whether to place the patient on a gluten-free diet and on further checkups should be taken together with the paediatric gastroenterologist (B).

Other Forms of Diabetes in Children and Adolescents

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Type 2 Diabetes

Type 2 diabetes should be diagnosed in adolescents on the basis of the normal range for fasting glucose and the OGTT using the standard or reference method (A).
If the test result meets either of the following conditions but the patient is asymptomatic, the result should be confirmed by another test on some other day [92]:

- fasting glucose: > 126 mg/dL (> 7.0 mmol/L),
- OGTT: 2-h level > 200 mg/dL (> 11.1 mmol/L).

Indications for distinguishing between type 2 and type 1 diabetes can be delivered by the following additional laboratory tests (0):

- C-peptide
- diabetic specific autoantibodies (GAD, IA2, ICA, IAA) [92, 93]

Therapy of adolescents for type 2 diabetes should aim to achieve fasting glucose levels under 126 mg/dL and an HbA1c level under 7 % (A) [94, 95].

Oral antidiabetics have to be used when metabolism control by life style intervention proves to be insufficient. Metformin is the agent of first choice (A) [96 – 99].

Monogenetic Diabetes

In cases of definite suspicions, a genetic diagnosis of the most frequent MODY forms (© **Table 4**) should be conducted because of their significance for therapy and long-term prognosis (B).

For legal reasons, the patient must first be given full advice and explanations [100, 101].

Neonatal Diabetes Mellitus (NDM)

Neonatal diabetes mellitus (NDM) and the diabetes which appears in the first six months of life are special forms of genetically caused diabetes. There are two subgroups clinically speaking: transient (TNDM) and permanent (PNDM) neonatal diabetes mellitus.

A molecular genetic analysis should be conducted In cases of neonatal diabetes mellitus which cannot be clarified and in those which manifest themselves in the first six months of life because this analysis can have decisive therapeutic consequences (B) [103 – 105].

Diabetes with Cystic Fibrosis

Since it is difficult to recognise diabetes in cases of cystic fibrosis, children with cystic fibrosis should receive an oral glucose tolerance test once a year when they have reached the age of ten. (B) [106].

Treatment of CFRD should be commenced when a diagnosis of diabetes has been confirmed (A) [106-109].

This therapy of CF related diabetes should be based on insulin. There is currently no sufficient evidence for the efficacy of oral antidiabetics. (A) [110].

When diabetes is diagnosed in cases of cystic fibrosis, the patient should be put on a high-calorie, high fat content diet. Reduction of calories is contraindicated (A) [111].

Table 4 The most frequent MODY forms and their clinical characteristics [100, 102].

MODY type (international proportion in %) mode of inheritance	Age in years at time of manifestation	Hyperglycaemia	Clinical picture
MODY 3 HNF-1α (20 – 50 %) autosomal dominant	14 (4 – 18)	severe	– strong blood sugar rise in OGTT (> 90 mg/dL), low kidney threshold (frequent glucosuria with blood sugar levels < 180 mg/dL (10 mmol/L), – hyperglycaemia increases with age, – responds to sulfonylureas
MODY 2 glucokinase (20 – 50 %) autosomal dominant	10 (0 – 18)	mild	– often a chance finding, – fasting blood sugar usually low, – increased between 99_144 mg/dL, (5.5 – 8 mmol/L), – blood sugar increase in OGTT low (approx. < 63 mg/dL or 3.5 mmol/L) – no blood sugar deterioration with increasing age – rarely micro or macrovascular complications, also without medicinal therapy
MODY 1 HNF-4α (1 – 5 %)	17 (5 – 18)	considerable	similar to HNF-1α but kidney threshold normal, responds to sulfonylureas

1. exclusion of pancreatic insufficiency
   - sonography to exclude pancreatic aplasia
   - determination of elastase in feces to exclude exocrine pancreatic insufficiency
2. if sonograph unremarkable or not usable:
   - determination of diabetes specific autoantibodies (GAD, IA2, ICA, IAA)
3. if sonograph unremarkable or not usable, autoantibodies negative and elastase in feces normal: conduct molecular-genetic analyses for differential diagnosis of:
   - abnormalities of chromosome 6q24 (TNDM)
   - mutations of the KCNJ11 gene (PNDM, TNDM)
   - mutations of the ABCC8 gene (PNDM, TNDM)
   - mutations of the insulin gene (PNDM)
4. in case of low elastase in feces with negative molecular genetic analysis regarding chromosomes 6q24, KCNJ11, ABCC and the insulin gene and negative or positive autoantibodies, examine for less frequent genetic disease/ genetic syndrome

Table 5 Diagnostic approach with diabetes manifestation up to age 6 months, possibly age 1 year.

Abbreviations

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Abbreviation	Explanation
KCL	potassium chloride
DGpRP	German Society for Paediatric Rehabilitation and Prevention
BG	blood glucose
NF	low frequency
APE	Paediatric Endocrinology Study Group
C-Peptid	connecting peptide
ACE	Angiotensin Converting Enzyme
ABCC8 gene	Gene Localisation for Sulfonylurea Receptor 1
ACR	albumin creatinine ratio
ÄZQ	Medical Centre for Quality in Medicine
AGPD	Paediatric Diabetology Study Group
AT-1 blocker	angiotensin type 1 receptor blocker
BAR	German Federal Study Group for Rehabilitation
BdKJ	German Association of Diabetic Children and Adolescents
BP	blood pressure
BMI	body mass index
bpm	beats per minute
CF	Cystic Fibrosis
CFRD	Cystic Fibrosis Related Diabetes
CK	creatine kinase
DAG	German Obesity Association
DDG	German Diabetes Association
DELBI	German Instrument for Assessing Guidelines
DGE	German Nutrition Association
DGEM	German Association for Nutritional Medicine
DiabetesDE	Diabetes Germany
DPV	Diabetes Patient Documenation
fT4	free thyroxin
GAD	glutamate decarboxylase
HbA1c	glycosylated hemoglobin
HDL	high density lipoprotein
IA2	tyrosine phosphatase IA2 antibody
IAA	insulin autoantibody
ICA	islet cell antibodies
ICT	intensified conventional therapy
KCNJ11	potassium inwardly-rectifying channel, subfamily J, member 11
LDL	low density lipoprotein
MODY	maturity onset diabetes of the young
MRT	magnetic resonance tomography
NaCL	sodium chloride
NPH-Insulin	neutral protamine Hagedorn insulin
OGTT	oral glucose tolerance test
PDM	permanent neonatal diabetes mellitus
pH	potentia hydrogenii (effectiveness of hydrogen) = negative decadic logarithm of hydrogen ion activity
SGB	German Social Law Book
STIKO	Standing Committee on Vaccination of the Federal Republic of Germany
Tg	thyreoglobulin
TNDM	transient neonatal diabetes mellitus
TPO-AK	thyroid peroxidase antibody
TSH	thyroid stimulating hormone/thyrotropin

Affiliations

1 Klinik für Kinder- und Jugendmedizin, Universitätsklinikum Tübingen
2 Klinik für Kinder und Jugendliche, Evangelisches Krankenhaus GmbH, Oberhausen
3 Bund diabetischer Kinder und Jugendlicher e. V., Kaiserslautern
4 Diabetes-Zentrum für Kinder und Jugendliche, Kinderkrankenhaus auf der Bult, Hannover
5 Altonaer Kinderkrankenhaus gGmbH, Hamburg
6 Kindermedizinisches Versorgungszentrum am Wilhelmstift, Hamburg
7 Abt. Epidemiologie, Universitätsklinikum Ulm
8 Sektion Endokrinologie und Diabetologie, RWTH Aachen
9 Universitätsklinik und Poliklinik für Kinder und Jugendliche, Leipzig
10 Kinder- und Jugendklinik des Universitätsklinikums Erlangen
11 Medizinische Hochschule, Medizinische Psychologie, Hannover
12 Katholisches Kinderkrankenhaus Wilhelmstift, Hamburg
13 Klinikum Bremen-Mitte gGmbH, Zentrum für Kinderheilkunde und Jugendmedizin, Bremen
14 Klinik und Poliklinik für Kinder- und Jugendmedizin, Universitätsklinikum Carl Gustav Carus, Dresden
15 Klinik für Kinder- und Jugendmedizin, Universitätsklinikum Schleswig-Holstein, Campus Lübeck
16 Bundesverband Bunter Kreis e. V., Institut für Sozialmedizin in der Pädiatrie, Augsburg
17 Fachklinik Sylt für Kinder und Jugendliche, Westerland
18 Diabetologische Schwerpunktpraxis, Münster
19 Klinik für allgemeine Pädiatrie, Universitätsklinikum Schleswig-Holstein, Campus Kiel

References

1 *Scherbaum WA, Kerner W.* Evidenzbasierte Leitlinie der DDG – Therapie des Diabetes mellitus Typ 1. In: Martin S, Dreyer M, Kiess W, Lüdecke HJ, Müller UA, Schatz W. Deutsche Diabetes Gesellschaft (DDG); 2007
2 *Neu A, Willasch A, Ehehalt S. et al.* Prävalenz und Altersverteilung des Diabetes mellitus im Kindesalter in Deutschland. Monatsschr Kinderheilkd 2002; 150: 196–200
3 *Rosenbauer J, Icks A, Grabert M. et al.* Hohe Prävalenz des Typ-1-Diabetes mellitus im Kindes- und Jugendalter in Deutschland (Abstract). Kinder-Jugendmed 2002; 2
4 *Ehehalt S, Blumenstock G, Willasch AM. et al.* Continuous rise in incidence of childhood Type 1 diabetes in Germany. Diabet Med 2008; 25: 755–757
5 *Neu A, Ehehalt S, Willasch A. et al.* Rising incidence of type 1 diabetes in Germany: 12-year trend analysis in children 0–14 years of age. Diabetes Care 2001; 24: 785–786
6 *Rosenbauer J, Icks A, Schmitter D. et al.* Incidence of childhood Type I diabetes mellitus is increasing at all ages in Germany. Diabetologia 2002; 45: 457–458
7 *Kurth BM, Schaffrath RA.* Die Verbreitung von Übergewicht und Adipositas bei Kindern und Jugendlichen in Deutschland. Ergebnisse des bundesweiten Kinder- und Jugendgesundheitssurveys (KiGGS). Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 2007; 50: 736–743
8 *Kromeyer-Hauschild K, Wabitsch M, Kunze D. et al.* Perzentile für den Body-Mass-Index für das Kindes- und Jugendalter unter Heranziehung verschiedener deutscher Stichproben. Monatsschr Kinderheilkd 2001; 149: 807–818
9 *Rosenbauer J, Icks A, duPrel JB. et al.* Populationsbasierte Daten zur Inzidenz des Typ-2-Diabetes mellitus bei Kindern und Jugendlichen in Deutschland. Monatsschr Kinderheilkd 2003; 151: 71
10 *Neu A, Feldhahn L, Ehehalt S. et al.* Prevalence of type 2 diabetes and MODY in children and adolescents. A state-wide study in Baden-Wuerttemberg (Germany). Pediatr Diabetes 2005; 6: 27–28
11 Australasian Paediatric Endocrine Group, Department of Health and Ageing, National Health and Medical Research Council (NHMRC). Clinical practice guidelines: Type 1 diabetes in children and adolescents; 2005, EK IV

12 *Gale EA, Gillespie KM.* Diabetes and gender. Diabetologia 2001; 44: 3 – 15
13 *Rosenbloom AL, Schatz DA, Krischer JP. et al.* Therapeutic controversy: prevention and treatment of diabetes in children. J Clin Endocrinol Metab 2000; 85: 494 – 522
14 Clinical practice guidelines: Type 1 diabetes in children and adolescents; 2005, EK I b
15 Arbeitsgemeinschaft Adipositas im Kindes- und Jugendalter (AGA). Leitlinien. Verabschiedet auf der Konsensus-Konferenz der AGA am 06.10.2008. Deutsche Adipositas-Gesellschaft; 2008
16 *Bangstad HJ, Danne T, Deeb LC. et al.* Insulin treatment. ISPAD clinical practice consensus guidelines 2006–2007. Pediatr Diabetes 2007; 8: 88 – 102
17 Australasian Paediatric Endocrine Group, Department of Health and Ageing, National Health and Medical Research Council (NHMRC). Clinical practice guidelines: Type 1 diabetes in children and adolescents; 2005, EK II b-III
18 *Rewers M, Pihoker C, Donaghue K. et al.* Assessment and monitoring of glycemic control in children and adolescents with diabetes. Pediatr Diabetes 2007; 8: 408 – 418
19 *Cranston I, Lomas J, Maran A. et al.* Restoration of hypoglycaemia awareness in patients with long-duration insulin-dependent diabetes. Lancet 1994; 344: 283 – 287
20 *Holl RW, Heinze E.* Dawn- oder Somogyi-Phänomen? Hohemorgendliche Nüchternblutzuckerwerte bei jugendlichen Typ-1-Diabetikern. Dtsch MedWochenschr 1992; 117: 1503 – 1507
21 *Hellems MA, Clarke WL.* Safe at school: a Virginia experience. Diabetes Care 2007; 30: 1396 – 1398
22 American Diabetes Association (ADA). Diabetes care in the school and day care setting. Diabetes Care 2007; 30 (Suppl 1): S66 – S73
23 *Nakhla M, Daneman D, Frank M. et al.* Translating transition: a critical review of the diabetes literature. J Pediatr Endocrinol Metab 2008; 21: 507 – 516
24 Australasian Paediatric Endocrine Group, Department of Health and Ageing, National Health and Medical Research Council (NHMRC). Clinical practice guidelines: Type 1 diabetes in children and adolescents; 2005
25 *Court JM, Cameron FJ, Berg-Kelly K. et al.* Diabetes in adolescence. Pediatr Diabetes 2008; 9: 255 – 262
26 *Brink S, Laffel L, Likitmaskul S. et al.* Sick day management in children and adolescents with diabetes. Pediatr Diabetes 2007; 8: 401 – 407
27 Diabetes Control and Complications Trial Research Group. The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the diabetes control and complications trial. Diabetes 1995; 44: 968 – 983
28 *White NH, Sun W, Cleary PA. et al.* Prolonged effect of intensive therapy on the risk of retinopathy complications in patients with type 1 diabetes mellitus: 10 years after the Diabetes Control and Complications Trial. Arch Ophthalmol 2008; 126: 1707 – 1715
29 *Nathan DM, Cleary PA, Backlund JY. et al.* Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 2005; 353: 2643 – 2653
30 *Musen G, Jacobson AM, Ryan CM. et al.* Impact of diabetes and its treatment on cognitive function among adolescents who participated in the Diabetes Control and Complications Trial. Diabetes Care 2008; 31: 1933 – 1938
31 *Bangstad HJ, Danne T, Deeb LC. et al.* Insulin treatment. ISPAD clinical practice consensus guidelines 2006–2007. Pediatr Diabetes 2007; 8: 88 – 102
32 *Danne T, Becker RH, Heise T. et al.* Pharmacokinetics, prandial glucose control, and safety of insulin glulisine in children and adolescents with type 1 diabetes. Diabetes Care 2005; 28: 2100 – 2105
33 *Mortensen HB, Lindholm A, Olsen BS. et al.* Rapid appearance and onset of action of insulin aspart in paediatric subjects with type 1 diabetes. Eur J Pediatr 2000; 159: 483 – 488
34 *Deeb LC, Holcombe JH, Brunelle R. et al.* Insulin lispro lowers postprandial glucose in prepubertal children with diabetes. Pediatrics 2001; 108: 1175 – 1179
35 *Plank J, Siebenhofer A, Berghold A. et al.* Systematic review and meta-analysis of short-acting insulin analogues in patients with diabetes mellitus. Arch Intern Med 2005; 165: 337 – 344
36 *Simpson D, McCormack PL, Keating GM. et al.* Insulin lispro: a review of its use in the management of diabetes mellitus. Drugs 2007; 67: 407 – 434
37 *Danne T, Aman J, Schober E. et al.* A comparison of postprandial and preprandial administration of insulin as part in children and adolescents with type 1 diabetes. Diabetes Care 2003; 26: 2359 – 2364
38 *Danne T, Datz N, Endahl L. et al.* Insulin detemir is characterized by a more reproducible pharmacokinetic profile than insulin glargine in children and adolescents with type 1 diabetes: results from a randomized, double-blind, controlled trial. Pediatr Diabetes 2008; 9: 554 – 560
39 *Thisted H, Johnsen SP, Rungby J.* An update on the long-acting insulin analogue glargine. Basic Clin Pharmacol Toxicol 2006; 99: 1 – 11
40 *Robertson KJ, Schoenle E, Gucev Z. et al.* Insulin detemir compared with NPH insulin in children and adolescents with Type 1 diabetes. Diabet Med 2007; 24: 27 – 34
41 *Phillip M, Battelino T, Rodriguez H. et al.* Use of insulin pump therapy in the pediatric age-group: consensus statement from the European Society for Paediatric Endocrinology, the Lawson Wilkins Pediatric Endocrine Society, and the International Society for Pediatric and Adolescent Diabetes, endorsed by the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2007; 30: 1653 – 1662
42 *Aslander-van Vliet E, Smart C. et al.* Nutritional management in childhood and adolescent diabetes. Pediatr Diabetes 2007; 8: 323 – 339
43 *Mann J, de Leeuw I, Hermansen K. et al.* Evidenz-basierte Ernährungsempfehlungen zur Behandlung und Prävention des Diabetes mellitus. Diabet Stoffw 2005; 14: 75 – 94
44 Deutsche Gesellschaft für Ernährung (DGE), Österreichische Gesellschaft für Ernährung (ÖGE), Schweizerische Gesellschaft für Ernährungsforschung (SGE), Schweizerische Vereinigung für Ernährung (SVE). Referenzwerte für die Nährstoffzufuhr. Neustadt/Weinstraße: Neuer Umschau Buchverl; 2008
45 *Bloomgarden ZT, Karmally W, Metzger MJ. et al.* Randomized, controlled trial of diabetic patient education: improved knowledge without improved metabolic status. Diabetes Care 1987; 10: 263 – 272
46 *deWeerdt I, Visser AP, Kok GJ. et al.* Randomized controlled multicentre evaluation of an education programme for insulin-treated diabetic patients: effects on metabolic control, quality of life, and costs of therapy. Diabet Med 1991; 8: 338 – 345
47 *Lange K, Sassmann H, von Schütz W. et al.* Prerequisites for age-appropriate education in type 1 diabetes: a model programme for paediatric diabetes education in Germany. Pediatr Diabetes 2007; 8 (Suppl 6): 63 – 71
48 *Swift PG.* Diabetes education. ISPAD clinical practice consensus guidelines 2006–2007. Pediatr Diabetes 2007; 8: 103 – 109
49 *Mensing C, Boucher J, Cypress M. et al.* National standards for diabetes self-management education. Task Force to Review and Revise the National Standards for Diabetes Self-Management Education Programs. Diabetes Care 2000; 23: 682 – 689
50 *Funnell MM, Brown TL, Childs BP. et al.* National standards for diabetes self-management education. Diabetes Care 2009; 32 (Suppl 1): S87 – S94
51 Bundesarbeitsgemeinschaft für Rehabilitation (BAR). Gemeinsames Rahmenkonzept der Gesetzlichen Krankenkassen und der Gesetzlichen Rentenversicherung für die Durchführung stationärer medizinischer Leistungen der Vorsorge und Rehabilitation für Kinder und Jugendliche; 2008, http://http://www.bar-frankfurt.de/upload/Rahmenkonzept.72dpi_435.pdf
52 *Fröhlich C, Hermann T, Koch S. et al.* Indikationen für eine stationäre Rehabilitation von Kindern und Jugendlichen mit Typ-1-Diabetes – eine bundesweite „DPV-Wiss"-Analyse. Diabet Stoffw 2008; 93
53 Verband Deutscher Rentenversicherungsträger (VDR). Rahmenkonzept zur medizinischen Rehabilitation von Kindern und Jugendlichen in der gesetzlichen Rentenversicherung. Empfehlungen des Verbandes Deutscher Rentenversicherungsträger; 1998, http://http://infomed.mds-ev.de/sindbad.nsf/f79a8096ad98496fc12571e700442be0/3ccf1982457e68f080256bc4003b2fa3/$FILE/ATTS1QCV/VDR_KiJu-Reha_1998.pdf
54 Deutsche Gesellschaft für pädiatrische Rehabilitation und Prävention. Leitlinie Rehabilitation Diabetes mellitus im Kindes- und Jugendalter; 2007, http://http://www.uni-duesseldorf.de/awmf/ll/070-003.htm
55 *Stachow R, Koch S, Fröhlich C. et al.* Effekte der stationären Rehabilitation von Kindern und Jugendlichen mit Diabetes mellitus Typ 1 – eine multizentrische DPV-Wiss-Analyse. Diabet Stoffw 2008: 59
56 *Stachow R, Schultz A, Kurzinsky U. et al.* Anti-Streß-Training für Kinder und Jugendliche mit Diabetes während der stationären Rehabilitation. Kindheit Entwicklung 2001; 10: 226 – 239

57 *Delamater AM.* Psychological care of children and adolescents with diabetes. Pediatr Diabetes 2007; 8: 340 – 348
58 *Forsander G, Persson B, Sundelin J. et al.* Metabolic control in children with insulin-dependent diabetes mellitus 5y after diagnosis. Early detection of patients at risk for poor metabolic control. Acta Paediatr 1998; 87: 857 – 864
59 *Hürter A, Otten A.* Familien mit diabetischen Kindern und Jugendlichen: Psychische und soziale Probleme und der Wunsch nach psychologischer Hilfe im Vergleich mit anderen chronischen Erkrankungen. In: Roth R, Borkenstein M eds. Psychosoziale Aspekte in der Betreuung von Kindern und Jugendlichen mit Diabetes. Basel: Karger; 1991: 150 – 159
60 *Sundelin J, Forsander G, Mattson SE.* Family-oriented support at the onset of diabetes mellitus: a comparison of two group conditions during 2 years following diagnosis. Acta Paediatr 1996; 85: 49 – 55
61 *Delamater AM, Bubb J, Davis SG. et al.* Randomized prospective study of self-management training with newly diagnosed diabetic children. Diabetes Care 1990; 13: 492 – 498
62 *Rydall AC, Rodin GM, Olmsted MP. et al.* Disordered eating behavior and microvascular complications in young women with insulin-dependent diabetes mellitus. N Engl J Med 1997; 336: 1849 – 1854
63 *Bryden KS, Neil A, Mayou RA. et al.* Eating habits, body weight, and insulin misuse. A longitudinal study of teenagers and young adults with type 1 diabetes. Diabetes Care 1999; 22: 1956 – 1960
64 *Nielsen S, Emborg C, Molbak AG.* Mortality in concurrent type 1 diabetes and anorexia nervosa. Diabetes Care 2002; 25: 309 – 312
65 *Meltzer LJ, Johnson SB, Prine JM. et al.* Disordered eating, body mass, and glycemic control in adolescents with type 1 diabetes. Diabetes Care 2001; 24: 678 – 682
66 *Colton P, Olmsted M, Daneman D. et al.* Disturbed eating behavior and eating disorders in preteen and early teenage girls with type 1 diabetes: a case-controlled study. Diabetes Care 2004; 27: 1654 – 1659
67 *Liss DS, Waller DA, Kennard BD. et al.* Psychiatric illness and family support in children and adolescents with diabetic ketoacidosis: a controlled study. J Am Acad Child Adolesc Psychiatry 1998; 37: 536 – 544
68 *Northam EA, Matthews LK, Anderson PJ. et al.* Psychiatric morbidity and health outcome in Type 1 diabetes – perspectives from a prospective longitudinal study. Diabet Med 2005; 22: 152 – 157
69 *Hood KK, Huestis S, Maher A. et al.* Depressive symptoms in children and adolescents with type 1 diabetes: association with diabetes-specific characteristics. Diabetes Care 2006; 29: 1389 – 1391
70 *Stewart SM, Rao U, Emslie GJ. et al.* Depressive symptoms predict hospitalization for adolescents with type 1 diabetes mellitus. Pediatrics 2005; 115: 1315 – 1319
71 *Lawrence JM, Standiford DA, Loots B. et al.* Prevalence and correlates of ressed mood among youth with diabetes: the SEARCH for Diabetes in Youth study. Pediatrics 2006; 117: 1348 – 1358
72 Australasian Paediatric Endocrine Group, Department of Health and Ageing, National Health and Medical Research Council (NHMRC). Clinical practice guidelines: Type 1 diabetes in children and adolescents; 2005, EK III/IV
73 *Glaser NS, Wootton-Gorges SL, Buonocore MH. et al.* Frequency of subclinical cerebral edema in children with diabetic ketoacidosis. Pediatr Diabetes 2006; 7: 75 – 80
74 *Fiordalisi I, Novotny WE, Holbert D. et al.* An 18-yr prospective study of pediatric diabetic ketoacidosis: an approach to minimizing the risk of brain herniation during treatment. Pediatr Diabetes 2007; 8: 142 – 149
75 *Wolfsdorf J, Craig ME, Daneman D. et al.* Diabetic ketoacidosis. Pediatr Diabetes 2007; 8: 28 – 43
76 *Edge JA, Jakes RW, Roy Y. et al.* The UK case-control study of cerebral oedema complicating diabetic ketoacidosis in children. Diabetologia 2006; 49: 2002 – 2009
77 *Wolfsdorf J, Craig ME, Daneman D. et al.* Diabetic ketoacidosis. Pediatr Diabetes 2007; 8: 28 – 43
78 *Hanas R, Lindgren F, Lindblad B.* Diabetic ketoacidosis and cerebral oedema in Sweden – a 2-year paediatric population study. Diabet Med 2007; 24: 1080 – 1085
79 *Roberts MD, Slover RH, Chase HP.* Diabetic ketoacidosis with intracerebral complications. Pediatr Diabetes 2001; 2: 109 – 114
80 *Franklin B, Liu J, Ginsberg-Fellner F.* Cerebral edema and ophthalmoplegia reversed by mannitol in a new case of insulin-dependent diabetes mellitus. Pediatrics 1982; 69: 87 – 90
81 *Banks CJ, Furyk JS.* Review article: hypertonic saline use in the emergency department. Emerg Med Australas 2008; 20: 294 – 305
82 *Clarke W, Jones T, Rewers A. et al.* Assessment and management of hypoglycaemia in children and adolescents with diabetes. Pediatr Diabetes 2008; 9: 165 – 174
83 Diabetes Control and Complications Trial Research Group. Effect of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus: Diabetes Control and Complications Trial. J Pediatr 1994; 125: 177 – 188
84 *Bangstad HJ, Danne T, Deeb LC. et al.* Insulin treatment. ISPAD clinical practice consensus guidelines 2006–2007. Pediatr Diabetes 2007; 8: 88 – 102
85 *Silverstein J, Klingensmith G, Copeland K. et al.* Care of children and adolescents with type 1 diabetes: a statement of the American Diabetes Association. Diabetes Care 2005; 28: 186 – 212
86 *Hill ID, Dirks MH, Liptak GS. et al.* Guideline for the diagnosis and treatment of celiac disease in children: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr 2005; 40: 1 – 19
87 *Silverstein J, Klingensmith G, Copeland K. et al.* Care of children and adolescents with type 1 diabetes: a statement of the American Diabetes Association. Diabetes Care 2005; 28: 186 – 212
88 *Kordonouri O, Maguire AM, Knip M. et al.* ISPAD Clinical Practice Consensus Guidelines 2006–2007. Other complications and associated conditions. Pediatr Diabetes 2007; 8: 171 – 176
89 *Hansen D, Brock-Jacobsen B, Lund E. et al.* Clinical benefit of a gluten-free diet in type 1 diabetic children with screening-detected celiac disease: a population-based screening study with 2 years' follow-up. Diabetes Care 2006; 29: 2452 – 2456
90 *Amin R, Murphy N, Edge J. et al.* A longitudinal study of the effects of a gluten-free diet on glycemic control and weight gain in subjects with type 1 diabetes and celiac disease. Diabetes Care 2002; 25: 1117 – 1122
91 *Lewis HM, Renaula TL, Garioch JJ. et al.* Protective effect of gluten-free diet against development of lymphoma in dermatitis herpetiformis. Br J Dermatol 1996; 135: 363 – 367
92 *Genuth S, Alberti KG, Bennett P. et al.* Follow-up report on the diagnosis of diabetes mellitus. Diabetes Care 2003; 26: 3160 – 3167
93 *Alberti G, Zimmet P, Shaw J. et al.* Type 2 diabetes in the young: the evolving epidemic: the international diabetes federation consensus workshop. Diabetes Care 2004; 27: 1798 – 1811
94 UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group Lancet 1998; 352: 837 – 853
95 *Holman RR, Paul SK, Bethel MA. et al.* 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008; 359: 1577 – 1589
96 *Shimazaki T, Kadowaki T, Ohyama Y. et al.* Hemoglobin A1c (HbA1c) predicts future drug treatment for diabetes mellitus: a follow-up study using routine clinical data in a Japanese university hospital. Transl Res 2007; 149: 196 – 204
97 UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34).. UK Prospective Diabetes Study (UKPDS) Group Lancet 1998; 352: 854 – 865
98 *Jones KL, Arslanian S, Peterokova VA. et al.* Effect of metformin in pediatric patients with type 2 diabetes: a randomized controlled trial. Diabetes Care 2002; 25: 89 – 94
99 *Gottschalk M, Danne T, Vlajnic A. et al.* Glimepiride versus metformin as monotherapy in pediatric patients with type 2 diabetes: a randomized, single-blind comparative study. Diabetes Care 2007; 30: 790 – 794
100 *Ellard S, Bellanne-Chantelot C, Hattersley AT.* Best practice guidelines for the molecular genetic diagnosis of maturity-onset diabetes of the young. Diabetologia 2008; 51: 546 – 553
101 *Badenhoop K, Kordonouri O, Machicao F.* Empfehlungen zur molekulargenetischen Diagnostik bei Verdacht auf MODY. DDG 2008
102 *Hattersley A, Bruining J, Shield J. et al.* ISPAD Clinical Practice Consensus Guidelines 2006–2007. The diagnosis and management of monogenic diabetes in children. Pediatr Diabetes 2006; 7: 352 – 360
103 *Flanagan SE, Edghill EL, Gloyn AL. et al.* Mutations in KCNJ11, which encodes Kir6.2, are a common cause of diabetes diagnosed in the first 6 months of life, with the phenotype determined by genotype. Diabetologia 2006; 49: 1190 – 1197

104 *Babenko AP, Polak M, Cave H. et al.* Activating mutations in the ABCC8 gene in neonatal diabetes mellitus. N Engl JMed 2006; 355: 456–466
105 *Klupa T, Kowalska I, Wyka K. et al.* Mutations in the ABCC8 gene are associated with a variable clinical phenotype. Clin Endocrinol (Oxf) 2008
106 *Lanng S, Thorsteinsson B, Lund-Andersen C. et al.* Diabetes mellitus in Danish cystic fibrosis patients: prevalence and late diabetic complications. Acta Paediatr 1994; 83: 72–77
107 *Nousia-Arvanitakis S, Galli-Tsinopoulou A, Karamouzis M.* Insulin improves clinical status of patients with cystic-fibrosis-related diabetes mellitus. Acta Paediatr 2001; 90: 515–519
108 *Rolon MA, Benali K, Munck A. et al.* Cystic fibrosis-related diabetes mellitus: clinical impact of prediabetes and effects of insulin therapy. Acta Paediatr 2001; 90: 860–867
109 *Dobson L, Hattersley AT, Tiley S. et al.* Clinical improvement in cystic fibrosis with early insulin treatment. Arch Dis Child 2002; 87: 430–431
110 *O'Riordan SM, Robinson PD, Donaghue KC. et al.* Management of cystic fibrosis-related diabetes. Pediatr Diabetes 2008; 9: 338–344
111 *Man SA, Andre JL, de Bachmann H. et al.* Blood pressure in childhood: pooled findings of six European studies. J Hypertens 1991; 9: 109–114b

Annex

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Grid for grading recommendations.

Grade of recommendation	Description	Syntax
A	strong recommendation	should / should not (German: "soll")
B	recommendation	ought to / ought not to (German: "sollte")
0	open recommendation	may be considered / no specific recommendation

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The guideline recommendations are based on systematic literature searches. A formal consensus was reached for each recommendation with more than 75 % acceptance.