Definition, Classification and Diagnosis of Diabetes Mellitus[1]

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Definition of diabetes mellitus

Diabetes mellitus is the collective term for heterogeneous metabolic disorders whose main finding is chronic hyperglycaemia. The cause is either a disturbed insulin secretion or various grades of insulin resistance or usually both.

Classification

Type 1 diabetes

- β-cell destruction that leads to an absolute insulin deficiency due to autoimmune ß-cell destruction,
- Checkpoint inhibitor-induced diabetes,
- Latent autoimmune diabetes in adults (LADA): a type of diabetes which usually slowly develops at an older age, classified as type 1 diabetes.

Type 2 diabetes

- Can range from a predominant insulin resistance with a relative insulin deficiency to a largely secretory defect with insulin resistance.
- Is often associated with other diseases (hypertension, obesity, dyslipidemia, atherosclerosis, chronic obstructive pulmonary disease (COPD), fatty liver, depression).

1 The team of authors has written the Clinical Practice Guidelines for the Commission for Laboratory Diagnostics in Diabetology/Kommission Labordiagnostik in der Diabetologie of the German Diabetes Society/ Deutsche Diabetes Gesellschaft (DDG) and the German Society for Clinical Chemistry and Laboratory Medicine (DGKL)/Deutschen Gesellschaft für Klinische Chemie und Laboratoriumsmedizin.

Other specific types of diabetes

- Exocrine pancreatic diseases (e. g. pancreatitis, cystic fibrosis, hemochromatosis, pancreatic cancer, after pancreatic surgery),
- Endocrinopathies (e. g. Cushing's syndrome, acromegaly, pheochromocytoma),
- Pharmacologically induced (e. g. glucocorticoids, neuroleptics, interferon-alpha, pentamidine),
- Infections
- Rare forms of autoimmune-mediated diabetes.
- Genetic defects:
  - of β-cell function (e. g., Maturity Onset Diabetes of the Young [MODY] and neonatal forms).
  - of insulin action
- Other genetic syndromes that may be associated with diabetes.

Gestational diabetes

Hyperglycemia that occurs or is diagnosed for the first time during pregnancy [1].

Diagnosis

Diagnostic criteria

Diabetes mellitus

The diagnostic criteria listed are in accordance with the recommendations of the international diabetes associations (International Diabetes Federation [IDF], American Diabetes Association [ADA], European Association for the Study of Diabetes [EASD], etc.) and the World Health Organization (WHO).

Measurand is the venous plasma glucose:

- Occasional plasma glucose value of ≥ 11.1 mmol/l (≥ 200 mg/dl), or
- Fasting plasma glucose of ≥ 7.0 mmol/l (≥ 126 mg/dl) (fasting time 8–12 h), or
- oral glucose tolerance test (OGTT) 2-h value in venous plasma ≥ 11.1 mmol/l (≥ 200 mg/dl) (for specifications for the procedure see ▶ **Tab. 2**), or

Measured variable HbA_{1c} :

- HbA_{1c} ≥ 48 mmol/mol Hb (HbA_{1c} value ≥ 6.5 %),

Abnormally-elevated fasting glucose levels

Impaired fasting glucose (IFG) for the fasting glucose range of 5.6-6.9 mmol/l (100-125 mg/dl) in venous plasma.

Impaired glucose tolerance

Impaired glucose tolerance (IGT) corresponds to a 2-h plasma glucose value oGTT in the range of 7.8-11.0 mmol/l (140-199 mg/dl) with fasting glucose values of < 5.6-6.9 mmol/l (100-125 mg/dl).

Many people with a glucose tolerance disorder have IFG and IGT. Both conditions must be met. In recommendations from many diabetes societies, an HbA_{1c} value of 39-48 mmol/mol Hb (5.7-6.4 %) is referred to as "prediabetes" (see ▶ **Tab. 4** for age dependence of the HbA_{1c} value).

Gestational diabetes

The cut-offs in the oGTT given in ▶ **Tab. 1** are based on the results of the HAPO study [1]. They differ only slightly from the previously valid values. Actual one too-high value is enough for diagnosis, whereas previously two values had to be high.

In pregnant women in whom the fasting plasma glucose value is close to the clinical decision value, the measurement should be repeated within one week.

Diagnostic procedure

The recommended diagnostic procedure is shown in ▶ **Fig 1**.

Only quality-assured laboratory methods are allowed to measure venous plasma glucose and HbA_{1c} for diagnosing diabetes.

This is defined in the guidelines of the German Medical Association for Quality Assurance in Laboratory Medical Examinations (Rili-BÄK) uniformly for central laboratories as well as for point-of-care testing (POCT) [2]. Participation in interlaboratory comparisons has so far not been mandatory for POCT methods used in medical offices. However, if POCT systems are approved by the manufacturer for diagnostic use, we also recommend successful participation in external interlaboratory comparison for use in diagnostics , Laboratory Diagnostics Commission of the DDG and DGKL recommends their application after successful participation in external interlaboratory comparisons.

The specifications for the performance of an oGTT are listed in ▶ **Tab. 2**.

Selected analytical aspects

Pre-analytics of glucose measurement

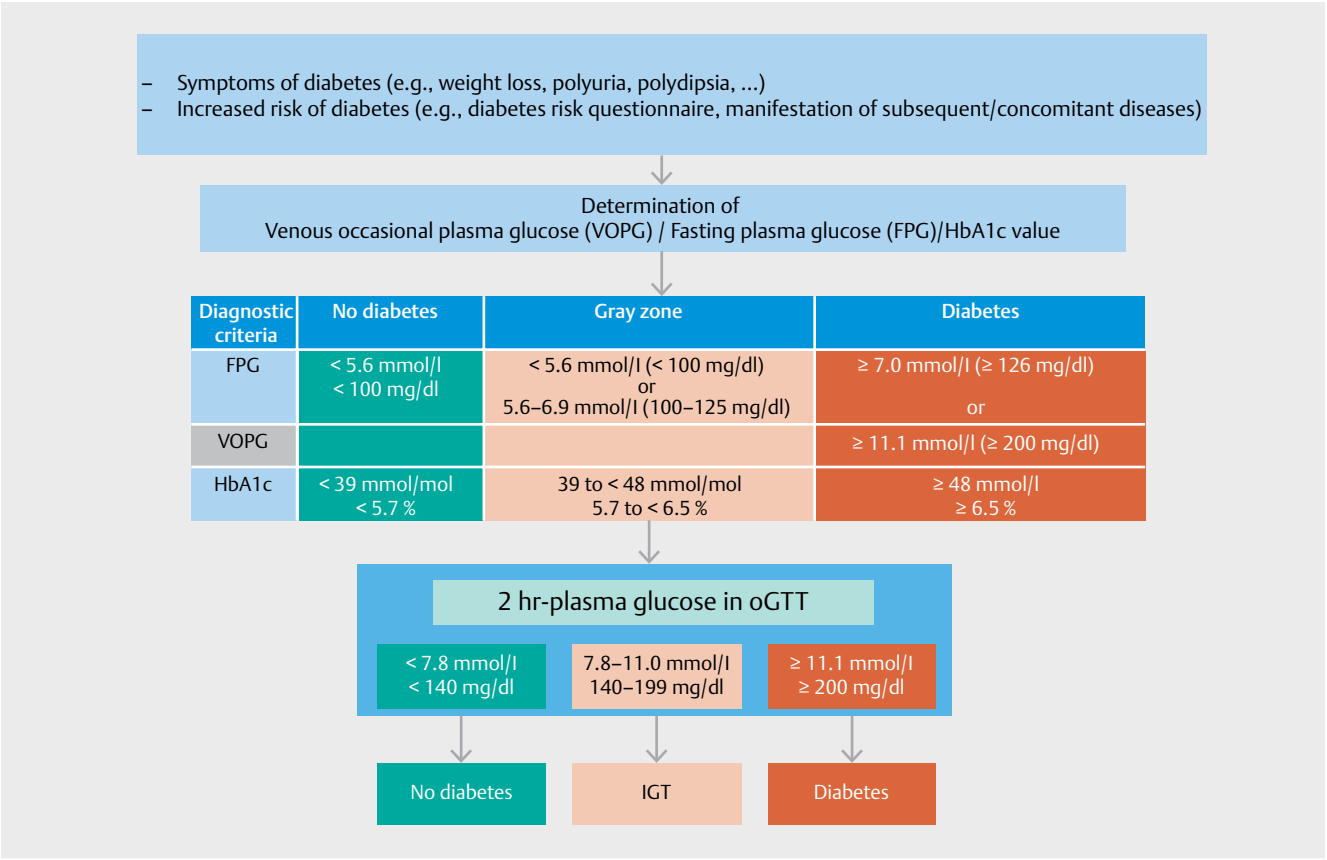
Adequate preanalytical handling of blood is very important. Precautions must be taken to ensure that glycolysis is completely inhibited in the blood samples by using suitable blood collection tubes. For this the addition of citrate plus fluoride is necessary; fluoride alone is not sufficient. The blood collection tubes with glycolysis inhibitors currently on the market exhibit various handling problems in ▶ **Tab. 3**.

Alternatively, it is recommended to centrifuge tubes immediately after blood collection without immediate and complete glycolysis inhibition. If a time window of 30 min until centrifugation is exceeded, the samples should be discarded due to the ongoing glycolysis (and therefore falsely lower glucose values). After centrifugation, the plasma supernatant must be separated from the blood cells. This occurs during centrifugation with a gel (gel tube). It is also possible to decant the plasma supernatant immediately after centrifugation.

Consistent and optimal preanalytical handling of the blood collection tubes might lead to a higher diabetes diagnosis rate of diabetes which however does not mean overdiagnosis.

▶ **Tab. 1** Diagnosis of gestational diabetes (75-g oGTT). Diabetes is confirmed when 1 criterion is met. For the pre-analytics of glucose determination, refer to section Pre-analytics of glucose measurement and the guideline for gestational diabetes.

	Venous plasma	
	mmol/l	mg/dl
Fasting	≥ 5.1	≥ 92
60 min	≥ 10.0	≥ 180
120 min	≥ 8.5	≥ 153



▶ **Fig. 1** Algorithm for the diagnosis of diabetes. For practical reasons, the Laboratory Diagnostics Commission of the Deutsche Diabetes Gesellschaft (DDG) and Deutsche Gesellschaft für Klinische Chemie und Laboratoriumsmedizin (DGKL) recommends simultaneous measurement of glucose and the HbA1c value, since these parameters complement each other (see ▶ **Tab. 5**). If plasma glucose and HbA1c are pathologically elevated (see text), no other determination needs to be made. In case of discrepant results of the different parameters, an oGTT should be performed. In practice, a repeat plasma glucose and HbA1c measurement can be done prior to an oGTT. A repeated measurement should be performed promptly, within 2 weeks. oGTT: oral glucose tolerance test; IFG: impaired fasting glucose; IGT: impaired glucose tolerance.

▶ **Tab. 2** Oral glucose tolerance test (oGTT).

Performing the 75-g oGTT-according to World Health Organization (WHO) guidelines
Performing the test in the morning • After 8-12 h of fasting with food, nicotine and alcohol abstinence • After a ≥ 3-day carbohydrate-rich diet (≥ 150 g carbohydrates per day) • Sitting or lying (no muscular effort); no smoking before or during the test
At time 0, ingestion of 75 g glucose (or equivalent amount of hydrolysed starch) in 250-300 ml water within 5 min. For children 1.75 g/kg (maximum 75 g) • Venous blood sampling at times 0 and 120 min • Proper sample processing and storage
Test contraindicated in intercurrent diseases, for gastrointestinal resection or gastrointestinal diseases with altered resorption or if diabetes mellitus has already been diagnosed.
The preparation of the glucose solution by the pharmacist/physician personally is rejected by the DDG for liability and medical reasons; see statement of Kommission Labordiagnostik in der Diabetologie (KLD) and Arbeitsgemeinschaft Diabetes & Technologie (AGDT) on the DDG website. As with all other laboratory tests, it is a prerequisite that the oGTT is performed adequately, including preparation of the patient.

HbA_{1c} for diagnosis

The use of a single HbA_{1c} value for diagnosis is currently not generally recommended, because HbA_{1c} values are influenced by various factors including an diabetes-independent increase with age (see ▶ **Tab. 4**, **5**) and, in particular, there are also a number of methodological problems. However, the methodological problems should be improved by the following measures:

The permissible deviation for internal quality control has been reduced from ± 10 % to 5 % and for external quality control from ± 18 % to ± 8 %. These guidelines of the German Medical Association (Rili-BÄK) have come into force in December 2021 with a two-year transition period.

If diabetes is diagnosed with an HbA_{1c} measurement, a confirmatory measurement with HbA_{1c} is not reasonable because the HbA_{1c} value can be influenced by various factors **(▶ Tab. 4, 5). HbA_{1c} is a haemoglobin** and is therefore influenced by various factors, including haematological factors (see info box).

To detect such influences on the HbA_{1c} value, an actual **blood count** should be available, especially if the HbA_{1c} value contributes to the diagnosis of diabetes mellitus. In principle, interpretation of the HbA_{1c} value without knowledge of the Hb is questionable.

▶ **Tab. 3** Commercially available blood collection tubes that achieve complete glycolysis inhibition by the addition of fluoride and citrate (current status see manufacturers' homepages).

Manufacturer	Product name	Correct filling absolutely necessary	Sufficient mixing required	Correction factor
Greiner bio-one	Vacuette® FC-Mix	No	10 times	No (granulate)
Kabe	Primavette®, KABEVETTE®	Yes	Few times	1.16 (liquid additive)
Sarstedt	S -Monovette GlucoEXACT®	Yes	Few times	1.16 (liquid additive)

Greiner bio-one tubes (Vacuette® FC-Mix) contain a granulate in the blood collection tubes. The tubes must be swivelled 10 times after filling the blood to achieve a sufficient solution and mixing with the glycolysis inhibitor. Experience with the blood collection tubes from Sarstedt (S-Monovette GlucoEXACT®) and Kabe (Primavette®, KABEVETTE®) shows that dilution errors occur when the tubes are not completely filled. The laboratory must reliably identify such tubes in order to identify and exclude from analysis tubes that are not correctly filled according to the manufacturer's specifications and to take into account the dilution factor of 1.16.

▶ **Tab. 4** Reference ranges (2.5th to 97.5th percentiles) for HbA_{1c} values collected in two large collectives in Germany.

	Roth J et al., 2016 [5] (n = 6783)	Masuch A et al., 2019 [9] (n = 8665)
< 40 y	27-41 mmol/mol (4.6-5.9 %)	20-42 mmol/mol (4.0-6.0 %)
40 < 60 y	29-44 mmol/mol (4.8-6.2 %)	21-44 mmol/mol (4.1-6.2 %)
≥ 60 y	31-46 mmol/mol (5.0-6.4 %)	25-49 mmol/mol (4.4-6.6 %)

▶ **Tab. 5** Comparison of selected factors relevant to the diagnosis of diabetes which influence fasting plasma glucose or HbA_{1c} (+ = influence, - = no or little influence).

	Glucose	HbA_{1c}
Muscle exertion	+	–
Food intake	+	–
Location of blood sampling	+	–
Haemoglobinopathies	–	+
Haematological disease	–	+
Erythrocyte turnover	–	+
Age	–	+
Individual variation from day to day	+ (12-15 %)	– (< 2 %)
Blood sample	+ (unstable in whole blood)	– (stable up to 7 days at RT)

NOTICE

Factors that lead to the influence of the HbA_{1c} or to disturbances of the HbA_{1c} measurement. (e. g. age dependence).
Factors which **influence** the HbA_{1c} value

- **decrease** (especially factors that increase erythrocyte turnover).
  - Haemolytic anaemia caused, e. g., by immunological processes, medications such as cephalosporins.
  - Treatment of iron or vitamin deficiency anaemia with appropriate medication
  - Severe hepatic or renal insufficiency
  - Hematologic diseases that increase erythrocyte turnover (thalassemias, pathologic haemoglobins).
- **increase** (especially factors that decrease erythrocyte turnover).
  - Anaemia, e. g., due to iron or vitamin deficiency (B12, folic acid).
  - Splenectomy
  - Age (see ▶ **Tab. 5**)
  - Ethnicity, f.e. HbA_{1c} value ~ 4 mmol/mol Hb (~ 0.4 %) higher in African Americans

- **Interference factors** that can falsify the measurement of HbA_{1c}.
- Most notably, haemoglobin variants that mismeasure HbA_{1c} , depending on the method used
- Most methods used today to measure HbA_{1c} are not interfered with by carbamylation (in severe renal insufficiency) or other modifications.

HbA_{1c} is **not suitable** for:

- Neonates (HbF ~ 90 %)
- Pregnant women for the diagnosis of gestational diabetes.
- Women up to about 2 months postpartum
- Hyperglycaemic drugs, e. g., glucocorticoids, psychotropic drugs if taken < 2 months
- Diseases of the pancreas ▶ **Tab. 7** incl. pancreatic surgery.
- Blood transfusions, blood donation, major bleeding (surgery, accidents).

Age dependency of HbA_{1c}

HbA_{1c} increases with age in people without diabetes [3–9]. This physiological increase can be 0.4-0.7 % (4-8 mmol/mol Hb) in absolute terms. This, in addition to methodological differences, limits the use of HbA_{1c} value for diabetes diagnosis, especially in the range below 53 mmol/mol Hb (7.0 %). ▶ **Tab. 4** shows reference values of HbA_{1c} level in non-diabetic adults of younger, middle and older age from two German populations [5, 9]. Thus, the 2.5th to 97.5th percentiles are given as the reference range. However, a measured value above the reference range does not necessarily have to be pathological [10].

Advantages and disadvantages of the glucose and HbA_{1c} measurands

The laboratory parameters glucose, especially fasting plasma glucose, and HbA_{1c}, which are approved for the diagnosis of diabetes, both have advantages and disadvantages. The advantages complement each other perfectly (▶ **Tab. 5**).

Quality assurance

The internal quality control must be carried out every working day with suitable control material. Successful participation in external quality assurance is required once per quarter.

This applies to all laboratory systems and to POCT "unit use" systems (individual test strips or cuvettes, according to the definition of the Rili-BÄK), which are also intended by the manufacturer for diagnosis.

Minimal difference

How should a single measured value be evaluated taking into account the measurement uncertainty of measurement results?

In the case of measurement results, there is generally the question of whether the deviation from the diagnostic cut-off is so far removed from this decision limit (i. e., greater than the minimum difference (MD), see below) that this measurement value can clearly be assessed as lower or higher. In such cases the MD should be used for assessment.

In order to meet clinical requirements, analytical variability should be expressed in absolute values at the decision limits. The so-called MD is a simple tool to illustrate the meaning of the random error to the user and is calculated from the standard deviation (SD) (MD = 2 × SD) (▶ **Fig. 2**) [18].

This MD, which can be obtained from the cooperative laboratory, gives concrete concentrations in absolute values above which a measured value differs from a diagnostic cut-off. At a fasting glucose cut-off of 7.0 mmol/L (126 mg/dl), the MD should not be greater than 0.7 mmol/l L (12.6 mg/dl). The same applies to an HbA_{1c} cut-off of 48 mmol/mol Hb (6.5 %). The MD should not be greater than 2 mmol/mol Hb (0.3 %).

Differential diagnosis of diabetes

The differential diagnostic criteria for the most common types of diabetes▶ **Tab. 6**.

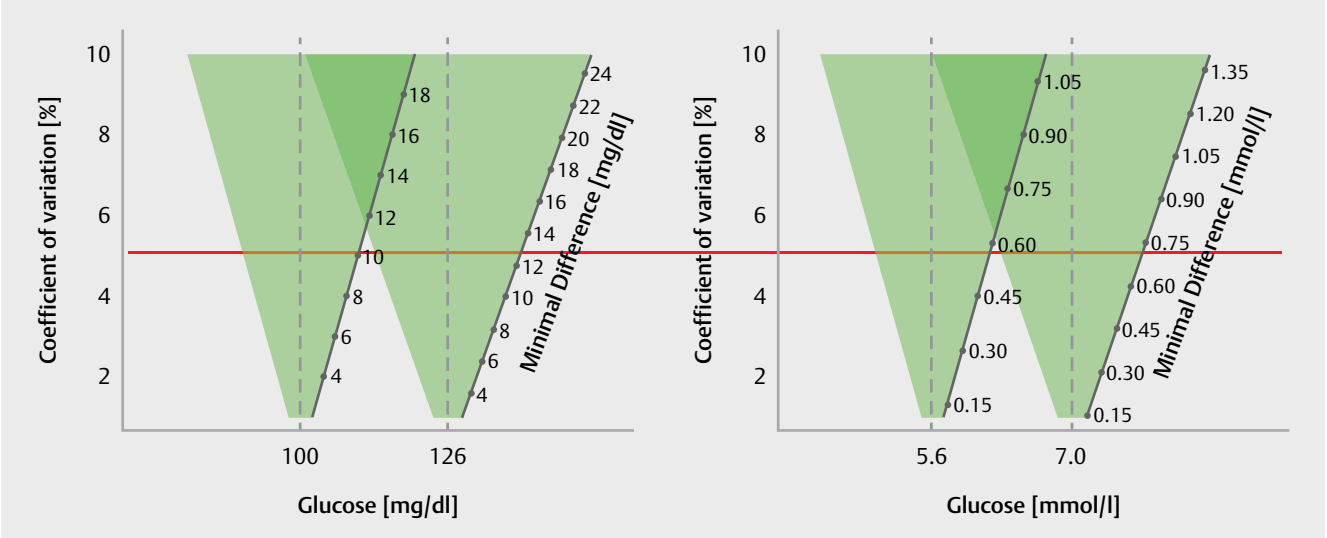
LADA (Latent Autoimmune Diabetes in Adults)

LADA (Latent Autoimmune Diabetes in Adults) is a slowly developing diabetes that occurs mainly in older age (> 35 years). Depending on the "genotype, phenotype, and immune status" (see ▶ **Fig. 3**), insulin dependence may develop more rapidly or more slowly. Reduction of excess weight, increase of physical activity, and oral antidiabetic drugs may also be effective, so that many patients have antibodies but phenotypically correspond to type 2 diabetes. These patients are also referred to as "double diabetes." Since the group of LADA is very heterogeneous, LADA has been regularly assigned to type 1 diabetes, although this is clinically justified only in the case of existing insulin dependence. In the other patients, the phenotype and also the drug therapy of type 2 diabetes are in the foreground. The pathophysiological mechanisms and diagnostic criteria are shown in ▶ **Fig. 3**.

Because of the often non-optimal specificity of autoantibody tests, there are both "true" patients with type 1 diabetes and patients with type 2 diabetes with false positive antibody tests in the heterogeneous group of LADA patients.

MODY

The term MODY (Maturity Onset Diabetes of the Young) is used to describe types of diabetes that are usually diagnosed from adolescence to adulthood and are caused by known genetic mutations. The diagnostic algorithm of the main MODY forms is shown in ▶ **Fig. 4**.

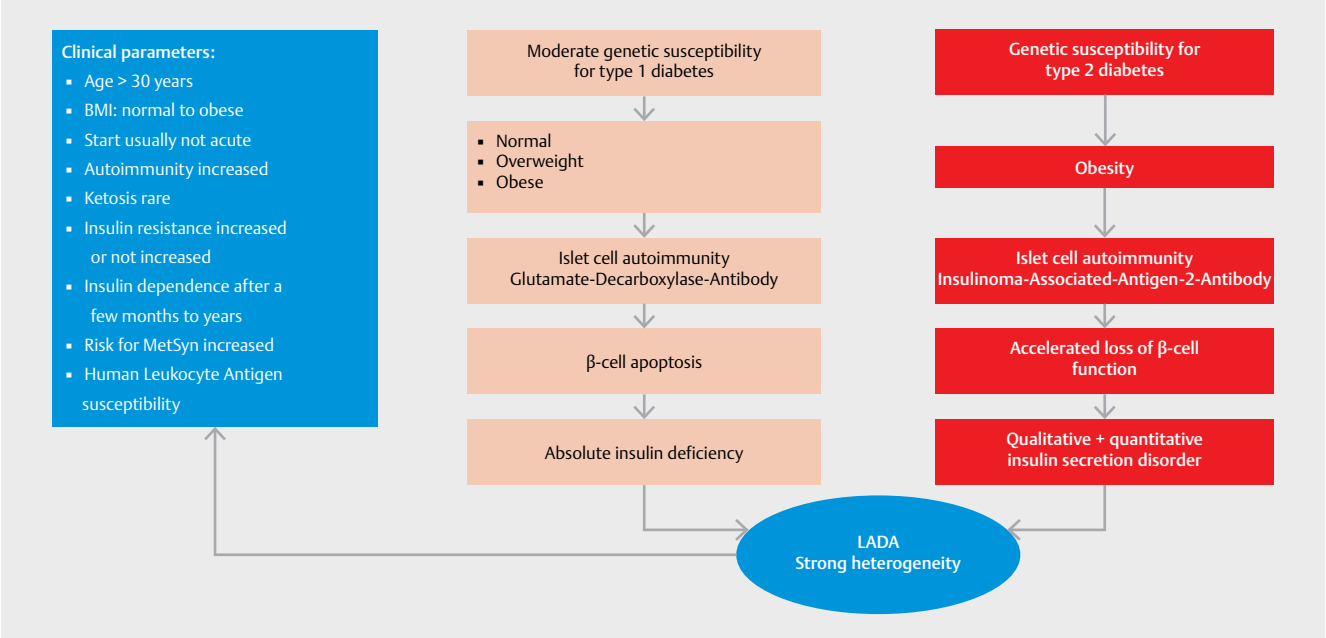


▶ **Fig. 2** Minimal difference, expressed in the unit of glucose determination (mg/dl or mmol/l) for the diagnostic cut-offs considered a function of the coefficient of variation. If the measured values are below the overlapping area of the drawn funnels, the diagnostic cut-offs can be analytically differentiated from each other and thus used for the diagnosis.

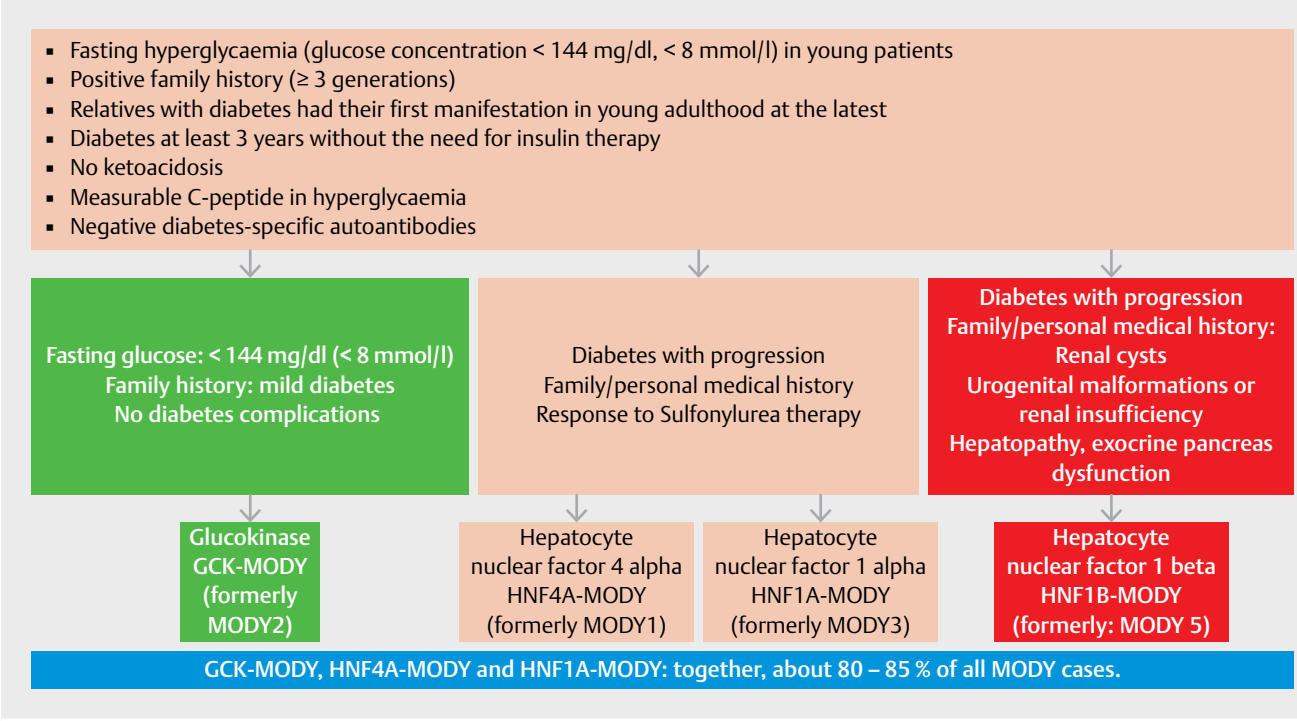
▶ **Tab. 6** Differential diagnostic criteria for common diabetes types at diagnosis. Data according to National Care Guideline Type 2 Diabetes; www.versorgungsleitlinien.de.

	Type 1 diabetes[1]	Type 2 Diabetes	MODYs
Aetiology	Autoimmune, genetic predisposition	Genetic predisposition, multifactorial	Monogenic
Heredity	Variable	Variable	Autosomal dominant; diabetes in ≥ 3 generations
Frequency among all diabetes types	5-10 %	90-95 %	Approx. 2 %
Pathogenesis	Autoantibodies, absolute insulin deficiency	Insulin resistance and secretion disorder up to insulin deficiency	Mutation of genes of transcription factors or glucokinase of the β-cells
Typical age of manifestation	Childhood to adulthood	Adulthood	Adolescence to early adulthood
Clinical manifestation	Acute polyuria, polydipsia, severe hyperglycaemia, ketoacidosis	Slow onset, often secondary diseases, moderate hyperglycaemia	Slow onset, variable hyperglycaemia
Comorbidities	Autoimmune thyroiditis, celiac disease	Visceral obesity, hypertension, Diabetes (also called Metabolic Syndrome)	Renal cysts depending on MODY type
Tendency to ketosis	Yes	No	No
Body weight	Normal weight	Overweight	Normal weight
Plasma insulin/C-peptide HOMA-B[2]	Reduced to lacking	Often high at beginning, then reduced	Mostly diminished
Autoantibodies	Yes	No	No
Insulin resistance HOMA-R[3]	No	Yes	No
Therapy	Insulin	Lifestyle modification measures, oral antidiabetics, insulin	Possibly none, OADs, insulin (depending on MODY type)

[1] Latent insulin-dependent diabetes in adulthood (LADA) is associated with a slow loss of beta cell function. LADA has a rapid failure of oral antidiabetics. If LADA is suspected, determination of autoantibodies typical for diabetes is recommended. [2,3] HOMA-B or Homa-R Homeostasis Model Assessment to quantify the β- cell reserve[2] and insulin resistance[3]; OADs = oral antidiabetic drugs. MODY = Maturity Onset Diabetes of the Young.



▶ **Fig. 3** Pathophysiological mechanisms and diagnostic criteria of Latent Autoimmune Diabetes in Adults. Data source: [11]. BMI = Body Mass Index, LADA = Latent insulin-dependent diabetes in adulthood



▶ **Fig. 4** Diagnostic algorithm of the most important MODY forms. Data source: [12] and MODY Probability Calculator (www.diabetesgenes.org/mody-probability-calculator) MODY = Maturity Onset Diabetes of the Young.

▶ **Tab. 7** Diagnosis of a diabetes due to an exocrine pancreas disease [1].

Criteria	expression
Main criteria (all must be present)	• Exocrine pancreatic insufficiency (documented by stool tests for elastase-1 or a direct functional test) • Pathological imaging of the pancreas (endosonography, Magnetic Resonance Imaging [MRI], computed tomography [CT]) • Lack of markers for type 1 diabetes
Additional criteria	• Impaired beta cell function (e. g. Homeostasis Model Assessment to quantify the β- cell reserve [HOMA-B], C-peptide glucose quotient) • No highly increased insulin resistance (e. g. Homeostasis Model Assessment to quantify the insulin resistance [HOMA-IR]) • Reduced incretin secretion (e. g. Glucagon-like peptide-1 (GLP-1), pancreatic polypeptide) • Low serum values of fat-soluble vitamins (A, D, E and K)

Pancreopriver diabetes mellitus

Diabetes that develops due to diseases of the pancreas is subsumed under the term pancreopriver diabetes mellitus. The diagnostic criteria are listed in ▶ **Tab. 7**.

Screening

For primary screening for diabetes, a diabetes risk test is recommended.

The following questionnaires are recommended:

- German Diabetes Risk Score (https://drs.dife.de/),
- FINDRISK Questionnaire (https://www.diabetesstiftung.de/findrisk).

In the case of high questionnaire scores, manifested cardiovascular disease or the presence of overweight with other risk factors, e. g. hypertension, dyslipidaemia (elevated triglyceride or LDL cholesterol or decreased HDL cholesterol), or a positive family history of type 2 diabetes in first-degree relatives, gestational diabetes or PCO (polycystic ovary syndrome), or non-alcoholic fatty liver as described in ▶ **Fig. 1**.

Although a lot of data on the prevalence of diabetes mellitus has been collected in various regions in Germany, there is no comprehensive screening for diabetes in hospitalized patients. According to a study carried out by the University Hospital of Tübingen, 24 % of newly admitted patients had prediabetes and 22 % manifested diabetes. Every 6th patients with diabetes had not been diagnosed [14]. The authors therefore recommend screening for every admitted patient over 50 years of age for diabetes.

Outlook

A number of studies indicate that the 1-h value has a higher predictive value for type 2 diabetes than the 2-h value [15, 16]. A petition has even been published calling for the 2-h value to be replaced by the 1-h value (≥ 8.6 mmol/L = 155 mg/dl) in the oGTT [17].

INFORMATION/LINKS

Addresses on the Internet
http://www.deutsche-diabetes-gesellschaft.de

- Current version of the evidence-based guidelines: https://www.deutsche-diabetes-gesellschaft.de/leitlinien.html

Conflict of Interest

A. Petersmann received consulting and contract fees from Tosoh Bioscience, Radiometer, Roche Diagnostics, Nova Biomedical, Siemens Healthineers, Becton Dickinson.; D. Müller-Wieland declares potential conflicts of interest: Member of Advisory Boards and has received lecture fees: Amarin, Amgen, Boehringer Ingelheim, Daiichi-Sankyo, Lilly, MSD, AstraZeneca, Novo Nordisk, Novartis, Sanofi.; U.A. Müller has not received any personal fees or travel expenses from pharmaceutical companies. Public declaration of interests: https://www.akdae.de/Kommission/Organisation/Mitglieder/DoI/Mueller.pdf ; R. Landgraf declares the following potential conflicts of interest: Advisory Boards: Lilly Deutschland, Novo Nordisk Pharma; presentation fees: AstraZeneca, Berlin Chemie, Lilly Deutschland, Novo Nordisk Pharma. Other activities: Authorized representative of the Executive Board of the German Diabetes Foundation, Steering Committee for the Development and Updating of the National Care Guidelines for Diabetes. M. Nauck received consulting and contract fees from Tosoh Bioscience, Radiometer, Roche Diagnostics, Nova Biomedical, Siemens Healthineers, Becton Dickinson.; G. Freckmann is medical director and managing director of the IfDT (Institut für Diabetes-Technologie Forschungs- und Entwicklungsgesellschaft mbH at the University of Ulm, Ulm), which carries out clinical studies on medical products for diabetes therapy on its own initiative or on behalf of various companies. GF/IDT has received lecture/consultancy fees from Abbott, Ascensia, Dexcom, LifeScan, Menarini Diagnostics, Metronom Health, Novo Nordisk, Roche, Sanofi, Sensile and Ypsomed.; L. Heinemann is a shareholder of Profil Institut für Stoffwechselforschung GmbH, Neuss. He is a consultant to a number of companies developing new diagnostic and therapeutic options for diabetes therapy.; E. Schleicher declares no conflict of interest.

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