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DIABETES MELLITUS [EASA.2022.C20]

D-1.1 Review of Diagnostic Measures

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SUMMARY

Diabetes is a chronic metabolic disorder characterized by high blood sugar levels. Diabetes, as well as its treatment modalities, might be associated with unstable blood glucose levels (hyper- and hypoglycaemia), which both are associated with significant impact in the cognitive abilities.

Their effects can bring about incapacitation, which erodes safety margins and might disrupt normal operations. On a more critical level, they can lead to errors and affect decision making.

“PILOT AND ATCO AEROMEDICAL FITNESS - DIABETES MELLITUS” is a research project implemented by the European Union Aviation Safety Agency (EASA) and funded under the framework of the European Union’s Horizon Europe research and innovation programme.

The project aims to provide evidence-based recommendations for practice standards as well as new medical developments regarding the diagnosis, treatment and complication of diabetes mellitus and its treatment modalities. These findings will be applied to better understand issues which could pose a safety risk in aviation. and would consequently lead to pilot and air traffic control officers (ATCOs) unfitness or the limitation of their license privileges for safety purposes.

The purpose of this “Review of Diagnostic Measures” is to give an overview of existing evidence regarding the classification and diagnostic measures for Diabetes Mellitus. Wherever possible, remarks have been added to draw attention to what this means for pilots and ATCOs living with diabetes.

DESCRIPTION OF WORK

The following report provides an overview of the existing evidence regarding the classification and diagnostic measures for Diabetes Mellitus.

To compile the report, a thorough literature search was performed in major databases (Scopus, Embase, Web of Science, Google Scholar, MedLine/Pubmed). The grey literature was also thoroughly reviewed.

The experts refuted the idea of a Cochrane-type systematic review and decided that the most robust and up-to-date evidence is already present in the most recent consensus from the two most prestigious international diabetes societies, the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD). These were updated recently on type 1 and type 2 diabetes mellitus in consensus reports, respectively "The Management of Type 1 Diabetes in Adults. A Consensus Report by the ADA and the EASD"[1] and "Management of hyperglycaemia in type 2 diabetes in 2022. A consensus report by the ADA and EASD"[2]. The recommendations for topics that are not included in the consensus are based on the "Standards of Care in Diabetes—2023."[3].

The evidence is presented and applied with a specific focus on pilots and ATCOs.

ABBREVIATIONS

ADA - American Diabetes Association
EASD - European Association for the Study of Diabetes
DM – Diabetes Mellitus
T1DM – Type 1 Diabetes Mellitus
T2DM – Type 2 Diabetes Mellitus
FPG - fasting plasma glucose
2-h PG 2-h plasma glucose
OGTT - oral glucose tolerance test
IGT - impaired glucose tolerance
IFG - impaired fasting glucose
MODY - maturity-onset diabetes of the young
DSPN - Distal symmetric polyneuropathy
CAN - cardiovascular autonomic neuropathy
DPN - diabetic peripheral neuropathy
NCS - nerve conduction studies
PPDM - post-pancreatitis diabetes mellitus
GDM - gestational diabetes mellitus
UACR - urinary albumin-to-creatinine ratio
eGFR – estimated glomerular filtration rate

1. CLASSIFICATION

Diabetes is a heterogenic chronic metabolic disorder characterized by high blood sugar levels. Several subforms, with different causes exist and can be classified into four general categories. Each category has its own unique causes, risk factors, and treatment approaches.
The following general categories have been defined[3,4]:

1. Type 1 diabetes (due to autoimmune beta-cell destruction, usually leading to absolute insulin deficiency, including latent autoimmune diabetes of adulthood)
2. Type 2 diabetes (due to a non-autoimmune progressive loss of adequate beta-cell insulin secretion frequently on the background of insulin resistance and metabolic syndrome)
3. Specific types of diabetes due to other causes, e.g., monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young), diseases of the exocrine pancreas (such as cystic fibrosis and pancreatitis), and drug- or chemical-induced diabetes (such as with glucocorticoid use, in the treatment of HIV/AIDS, or after organ transplantation)
4. Gestational diabetes mellitus (diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation)

Diabetes is a condition that presents a broad spectrum of clinical manifestations and disease progression, thereby rendering it a complex and heterogeneous medical condition. Although type 1 and type 2 diabetes account for most diabetes cases, diagnosis of some patients remain uncertain. While it was conventionally believed that type 2 diabetes only affects older adults and type 1 diabetes only affects children, this is no longer true as both types can manifest in individuals of any age. The issue of misdiagnosis is also prevalent, and over time, the presence of beta-cell deficiency may become more apparent.[5]

2. CRITERIA FOR THE DIAGNOSIS OF DIABETES MELLITUS

According to ADA and the most recent Standards of Care, diabetes may be diagnosed based on plasma glucose criteria, either the fasting plasma glucose (FPG) value or the 2-h plasma glucose (2-h PG) value during a 75-g oral glucose tolerance test (OGTT), or HbA1c criteria[3–5]:

FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*
OR
2-h PG ≥200 mg/dL (11.1 mmol/L) during OGTT. The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*
OR
HbA1c ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
OR
In a patient with classic symptoms of hyperglycaemia or hyperglycaemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).
DCCT, Diabetes Control and Complications Trial; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; NGSP, National Glycohemoglobin Standardization Program; WHO, World Health Organization; 2-h PG, 2-h plasma glucose.
***In the absence of unequivocal hyperglycaemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples.**

It is crucial to bear in mind that factors such as individual or population variations may influence the accuracy of each method. Prevention interventions have primarily been assessed in individuals exhibiting impaired glucose tolerance (IGT) with or without elevated fasting glucose, as opposed to those demonstrating isolated impaired fasting glucose (IFG) or prediabetes identified through HbA1c criteria (see below- Type 2 diabetes).

The FPG and OGTT tests can both diagnose diabetes, but their results are not always consistent. Furthermore, HbA1c tests may differ from either the FPG or OGTT tests; if this occurs, the FPG and OGTT tests are more reliable for diagnosis. The OGTT test may detect more cases of prediabetes or diabetes than either FPG or HbA1c cut points. [6–10]

While the HbA1c test has lower sensitivity compared to other tests, it presents several benefits, such as not requiring fasting, displaying increased stability during pre-analytical phases, and experiencing fewer daily variations due to illness, stress, or diet. Consequently, despite detecting only 30% of diabetes cases identified in total through HbA1c, FPG, or 2-h PG tests, it was incorporated into routine diagnostic criteria in 2009 by an International Expert Committee.

Recommendations of the American Diabetes Association regarding HbA1c[5]:

- To avoid misdiagnosis or missed diagnosis, the HbA1c test should be performed using a method that is certified by the National Glycohemoglobin Standardization Program (NGSP) and standardized to the Diabetes Control and Complications Trial (DCCT) assay.
- Point-of-care HbA1c testing for diabetes screening and diagnosis should be restricted to U.S. Food and Drug Administration– approved devices at laboratories proficient in performing testing of moderate complexity or higher by trained personnel.
- Marked discordance between measured HbA1c and plasma glucose levels should raise the possibility of HbA1c assay interference and consideration of using an assay without interference or plasma blood glucose criteria to diagnose diabetes.
- In conditions associated with an altered relationship between HbA1c and glycemia, such as hemoglobinopathies including sickle cell disease, pregnancy (second and third trimesters and the postpartum period), glucose-6-phosphate dehydrogenase deficiency, HIV, haemodialysis, recent blood loss or transfusion, or erythropoietin therapy, only plasma blood glucose criteria should be used to diagnose diabetes.
- Adequate carbohydrate intake (at least 150 g/day) should be assured for 3 days prior to oral glucose tolerance testing as a screen for diabetes.

Specific advice for pilots and ATCOs

In principle, all diagnostic methods can also be used for pilots and ATCOs. However, the following points should be borne in mind:
- Fasting glycemia requires a fasting state and has been standardized in individuals after a night's rest.
- OGTT interpretation depends on this dynamic test being executed according to high standards (fasting for 8 hours before test, test duration of 2hours, when the subject needs to be in full physical and psychological rest) and requires specific logistics (experienced personnel for execution, space for conducting the test)
- Point of care testing for HbA1c exists (test results in minutes), but certified methods need to be used considering the implications. Thus, laboratory testing is preferred, which takes some time to get the test result.

Therefore, the easiest and best test for screening for diabetes in pilots and ATCOs is HbA1c measurement using a certified test, with confirmation for diagnosis using HbA1c on a second sample or using other test (fasting glycemia or OGTT) in case of abnormal value.

3. TYPE 1 DIABETES MELLITUS

Formerly referred to as "insulin-dependent diabetes" or "juvenile-onset diabetes," this subtype of diabetes accounts for 5–10% of diabetes diagnoses and is typically the result of cellular-mediated autoimmune destruction of pancreatic beta-cells. Assessment for the presence of autoimmune markers within individuals with this form of diabetes is critical and may include islet cell autoantibodies, as well as autoantibodies to GAD (GAD65), insulin, the tyrosine phosphatases IA-2 and IA-2β, and zinc transporter 8 (ZnT8). [3,5 11,12]

Through better insight in the pathogenesis of type 1 diabetes and the discovery of novel biomarkers, it has become clear that this disease thought to present only in childhood and adolescence can actually present at any age, with 50% of individuals diagnosed after the age of 18 years.[13]

Genetic predisposition is typically linked to HLA (HLA DR3/DR4) and Caucasian ethnicity is predisposing.
On the basis of genetics or presence of autoantibodies screening for type 1 diabetes can be performed identifying people in early stages, before presence of hyperglycaemia or in presence of mild dysglycemia. Disease modifying therapies that can delay the progression of the disease to frank diabetes are being introduced to the clinics (e.g. teplizumab). [3,5,17–19]

In recent years however, many people develop type 1 diabetes (with insulinopenia, absence of obesity/insulin resistance- see below type 2 diabetes) without presence of the typical ethnic or genetic predisposition, and sometimes even without presence of autoantibodies. Moreover, type 1 diabetes incidence and prevalence is increasing worldwide, with culprits as viruses being identified.[17]

Diagnosis of type 1 diabetes:

- Detection of autoimmunity (autoantibodies) will identify type 1 diabetes, sometimes in early stages, with normoglycemia still present (stage 1) or in the presence of dysglycemia (stage 2-prediabetes)
- Overt clinical type 1 diabetes (stage 3) is diagnosed using the criteria of hyperglycaemia described above (p. 7)

Specific advice for pilots and ATCOs

Persons with type 1 diabetes are treated with insulin right from the date of clinical diabetes manifestation. Until recently, insulin administration was not subject to feedback, allowing automated adaptation of the required insulin dose. As an imbalance between the administered insulin dose and the insulin requirement of the individual (increased with meals, decreased with exercise) might lead to hypoglycaemia, which, in turn, might be associated with cognitive problems that could lead to errors and affect decision making, to date pilots/ATCOs in Europe have been denied class 1 medical certificate, which is required for flying a commercial airplane. Due to the arrival of better insulins and ways to measure glucose levels in the blood, it was possible to establish a protocol ARA.MED.330, in some European countries, that have allowed people with type 1 diabetes to be pilots and ATCOs.
In present day, modern therapy of people living with T1D, is evolving to automated insulin delivery, where insulin pumps, connected to glucose sensors, will adapt the dose of insulin delivered on the basis of glucose

levels through artificial intelligence driven algorithms. These systems allow tight glycaemic control, while minimizing the risk of hypoglycaemia.

The subject of the present project is to have a update evidence base picture of the stat of the art of Diabetes diagnostic and treatment, with specific considerations for Pilots and ACTOs. The outcome of this research study may lead to the update of the EASA regulation for people with type 1 diabetes as to their fitness for execution their functions**.**

TYPE 2 DIABETES MELLITUS

Type 2 diabetes makes up 90-95% of all diabetes cases, making it the most common form. This type of diabetes is characterized by peripheral insulin resistance and relative insulin deficiency. People with type 2 diabetes do not have any other known causes of diabetes, and unlike type 1 diabetes, there is no autoimmune destruction of beta-cells. Most patients with type 2 diabetes are overweight or obese, contributing to a certain level of insulin resistance. However, even those who are not obese or overweight may have an increased percentage of body fat mainly located in the abdominal region, which heightens the risk of type 2 diabetes.

In individuals with type 2 diabetes, an increased risk of cardiovascular disease is present, and screening should not only focus on presence of hyperglycaemia, but include screening for cardiovascular risk factors (hypertension, obesity, hypercholesterolemia etc.) [3,5,6,9,10,18]

Diagnosis of type 2 diabetes:

- Overt clinical type 2 diabetes is diagnosed using the criteria of hyperglycaemia described above (p. p 7)
- Clinical profile (overweight/obesity, presence of metabolic syndrome)
- Absence of other forms of diabetes (exclusion diagnosis)

3.1 Prediabetes

"Prediabetes" is the term used for individuals whose glucose levels do not meet the criteria for diabetes but are too high to be considered normal**.**[5,18]

According to the most recent Standards of Care (ADA), prediabetes is characterized by the presence of[5,21]:

impaired fasting glucose (IFG): fasting plasma glucose levels that range from 100 to 125 mg/dL (from 5.6 to 6.9 mmol/L)
and/or
impaired glucose tolerance (IGT): 2-hour plasma glucose levels that range from 140 to 199 mg/dL (from 7.8 to 11.0 mmol/L) during a 75-g OGTT

and/or

an HbA1cHbA1c level between 5.7% and 6.4% (39-47 mmol/mol).

It is worth noting that the IFG lower limit is defined at 110 mg/dL (6.1 mmol/L) by the World Health Organization and various other diabetes organizations. Also, individuals with an HbA1c range of 5.7-6.4% (39-47 mmol/mol) can be identified as having prediabetes, and it is reasonable to consider this range as such.

3.2 Screening for Prediabetes and Type 2 Diabetes[5]

The American Diabetes Association suggests the following strategy in its 2023 Guidelines[5,21]:

- Screening for prediabetes and type 2 diabetes with an informal assessment of risk factors or validated risk calculator should be done in asymptomatic adults.
- Testing for prediabetes and/ or type 2 diabetes in asymptomatic people should be considered in adults of any age with overweight or obesity (BMI **≥**25 kg/m2 or **≥**23 kg/m2 in Asian individuals) who have one or more risk factors.
- For all people, screening should begin at age 35 years.

If tests are normal, repeated screening is recommended at a minimum of 3-year intervals is reasonable, but advisable to screen sooner than 3 y with symptoms or change in risk (i.e., weight gain).

To screen for prediabetes and type 2 diabetes, each of the following measurements will be appropriate: fasting plasma glucose, 2-h plasma glucose during 75-g oral glucose tolerance test, and HbA1c. In people with prediabetes and type 2 diabetes, identify and treat cardiovascular disease risk factors.

People with HIV should be screened for diabetes and prediabetes with a fasting glucose test before starting antiretroviral therapy, at the time of switching antiretroviral therapy, and 3–6 months after starting or switching antiretroviral therapy. If initial screening results are normal, fasting glucose should be checked annually.

3.3 Screening for diabetes or prediabetes in asymptomatic adults[5]

When screening is considered, the ADA guidelines of 2023 propose the following[5,21]:

1. Testing should be considered in adults with overweight or obesity (BMI ≥25 kg/m2 or ≥23 kg/m2 in Asian individuals) who have one or more of the following risk factors:
    - First-degree relative with diabetes
    - High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American and Pacific Islander)
    - History of CVD
    - Hypertension (≥140/90 mmHg or on therapy for hypertension)
    - HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L)
    - Individuals with polycystic ovary syndrome
    - Physical inactivity
    - Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
2. People with prediabetes (HbA1c ≥5.7% [39 mmol/mol], IGT, or IFG) should be tested yearly.
3. People who were diagnosed with GDM should have lifelong testing at least every 3 years.
4. For all other people, testing should begin at age 35 years.
5. If results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results and risk status.
6. People with HIV, CVD cardiovascular disease; GDM gestational diabetes mellitus; IFG impaired fasting glucose; IGT impaired glucose tolerance.

Specific advice for pilots and ATCOs

Most people with type 2 diabetes are not treated with insulin, but will manage to maintain tight glycaemic control by lifestyle modifications (introduction of exercise, intensification of healthy eating, weight reduction) or medications that do not carry a risk of hypoglycaemia (see advice on therapy). In this situation, no

contraindication for pilots or ATCOs should exist. Still, applicants with diabetes mellitus not requiring insulin will be assessed as unfit unless it can be demonstrated that blood sugar control has been achieved and is stable. (EASA, Easy Access Rules for Medical Requirements)

People with type 2 diabetes might receive types of hypoglycaemic medication that can induce hypoglycaemia (sulfonylurea or insulin, see advice on therapy), with consequences as impaired cognitive behaviour or effects on decision making cannot be completely ruled out, thus leading to the same objections for pilots and ATCOs as in the situation of type 1 diabetes (see above). To date, use of insulin or other medications that can cause hypoglycaemia, leads to most countries in Europe declaring pilots or ATCOs as unfit to execute their function.

Attention should be paid to comorbidities in people with type 2 diabetes being pilots and ATCOs who are declared fit to execute their function on the basis of their glycaemic control. Specific attention should be paid to presence of diabetic complications (see below), with testing for cardiovascular risk, visual acuity and sensory acuity. Those applicants who, in addition to having type 2 diabetes, are HIV positive may be assessed as fit subject to satisfactory aero-medical evaluation. Such applicants for a class 1 medical certificate shall be referred to the medical assessor of the licensing authority. (EASA, Easy Access Rules for Medical Requirements).

4. SPECIFIC TYPES OF DIABETES

4.1 Monogenic Diabetes Syndromes [3,19–23] [21,24–27]

Progressively genetic causes of diabetes are being identified. The group of people with diabetes who have a mutation or variant in a single gene is growing. Accurate diagnosis of monogenic forms of diabetes is crucial, as they are frequently misidentified as type 1 or type 2 diabetes, resulting in inappropriate or potentially harmful treatments and delays in diagnosing other family members.

Monogenic defects leading to beta-cell dysfunction, such as neonatal diabetes and maturity-onset diabetes of the young (MODY), still account for only a small portion of diabetes patients (<5%). Diabetes appearing within the first 6 months of life is labelled "neonatal" or "congenital" diabetes, and roughly 80-85% of these cases are found to have an underlying monogenic cause.

As "atypical diabetes" becomes more challenging to define due to the absence of a definitive set of tests for either type of diabetes, a MODY diagnosis should be considered for people with atypical diabetes and multiple family members affected by diabetes that does not fit the typical type 1 or type 2 diabetes profile.

According to the Standards of Care (ADA), the diagnosis of monogenic diabetes should be thought of in children and adults diagnosed with diabetes in early adulthood, given the following findings:

- Diabetes diagnosed within the first 6 months of life (with occasional cases presenting later, mostly INS and ABCC8 mutations)
- Diabetes without typical features of type 1 or type 2 diabetes (negative diabetes-associated autoantibodies, no obesity, lacking other metabolic features, especially with strong family history of diabetes)
- Stable, mild fasting hyperglycaemia (100-150 mg/dL [5.58.5 mmol/L]), stable HbA1c between 5.6% and 7.6% (between 38 and 60 mmol/mol), especially in the absence of obesity.

Genetic counselling should be offered to affected individuals and their families.

Diagnosis of Monogenic Diabetes:

- Overt clinical monogenic diabetes is diagnosed using the criteria of hyperglycaemia described above (p. 7)
- Clinical profile suggestive, in particular presence of family history.

Detection of variants/mutations of genes

4.2 PANCREATIC DIABETES OR DIABETES IN THE CONTEXT OF DISEASE OF THE EXOCRINE PANCREAS[3,5,28–30]

Pancreatic diabetes represents a unique type of diabetes whose manifestation arises out of structural and functional disruption to insulin secretion, which specifically results from damage to the exocrine pancreas. This specific type of diabetes is often misdiagnosed as type 2 diabetes. Hyperglycaemia resulting from compromised pancreatic function is commonly identified as type 3c diabetes or pancreoprivic diabetes.

The potential causes of pancreatic diabetes range from pancreatitis, trauma, or pancreatectomy to neoplasia, cystic fibrosis, hemochromatosis, fibro-calculous pancreatopathy, rare genetic disorders, and idiopathic forms. Even a solitary bout of pancreatitis may lead to post-pancreatitis diabetes mellitus (PPDM), and both acute and chronic pancreatitis are implicated in its onset.

An important feature of PPDM is the presence of pancreatic exocrine insufficiency, abnormal pancreatic imaging, and the absence of autoimmunity-associated with type 1 diabetes. In PPDM, there is a decrease in insulin and glucagon secretion, resulting in higher-than-normal insulin requirements.

Diagnosis of Pancreatic Diabetes:

- Overt clinical monogenic diabetes is diagnosed using the criteria of hyperglycaemia described above (p. 7)
- Clinical profile suggestive, in particular presence of pancreatic pathology or history thereof.

4.3 GESTATIONAL DIABETES MELLITUS[3,5,31–37]

The definition of gestational diabetes mellitus (GDM) previously encompassed any degree of glucose intolerance initially detected during pregnancy, regardless of the level of hyperglycaemia severity. While beneficial in standardized identification and classification of GDM, this definition is not without limitations.

Research data indicates that numerous GDM cases potentially harbour pre-existing hyperglycaemia that can be detected by routine screening before pregnancy. The severity of hyperglycaemia assumes significance in determining both short- and long-term maternal and foetal risks. With the increasing prevalence of obesity and type 2 diabetes among reproductive-aged individuals, an increasing number of pregnant women possess undiagnosed type 2 diabetes during early pregnancy.

The consequences of GDM pose risks for the mother, foetus, and newborn. More than 23,000 pregnant women took part in the ground-breaking Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) study, which revealed that, even within normal pregnancy levels, the risk of adverse maternal, foetal, and neonatal outcomes rose significantly as glycemia levels increased between 24-28 weeks of gestation.[31–33] The majority of adverse outcomes displayed no set risk threshold. Against the backdrop of these findings, the diagnostic protocols for GDM were thoughtfully scrutinized.

4.3.1 Diagnosis of and screening for GDM[5]:

4.3.1.1 One-step strategy

Perform a 75-g OGTT, with plasma glucose measurement when patient is fasting and at 1 and 2h, at 24–28 weeks of gestation in individuals not previously diagnosed with diabetes. The OGTT should be performed in the morning after an overnight fast of at least 8 h. The diagnosis of GDM is made when any of the following plasma glucose values are met or exceeded:

- Fasting: 92 mg/dL (5.1 mmol/L)
- 1 h: 180 mg/dL (10.0 mmol/L)
- 2 h: 153 mg/dL (8.5 mmol/L)

4.3.1.2 Two-step strategy

Step 1: Perform a 50-g GLT (non-fasting), with plasma glucose measurement at 1 h, at 24–28 weeks of gestation in individuals not previously diagnosed with diabetes.
If the plasma glucose level measured 1 h after the load is 130, 135, or 140 mg/dL (7.2, 7.5, or 7.8 mmol/L, respectively), proceed to a 100-g OGTT.

Step 2: The 100-g OGTT should be performed when the patient is fasting. The diagnosis of GDM is made when at least two* of the following four plasma glucose levels (measured fasting and at 1, 2, and 3 h during OGTT) are met or exceeded (Carpenter-Coustan criteria):

- Fasting: 95 mg/dL (5.3 mmol/L)
- 1 h: 180 mg/dL (10.0 mmol/L)
- 2 h: 155 mg/dL (8.6 mmol/L)
- 3 h: 140 mg/dL (7.8 mmol/L)

GDM, gestational diabetes mellitus; GLT, glucose load test; OGTT, oral glucose tolerance test.
*American College of Obstetricians and Gynaecologists accepts one abnormal value as valid criteria for the diagnosis.

4.4 Other forms

Many diseases (e.g., Cushing's disease, acromegaly), drugs (e.g., corticosteroids, antivirals) or diseases (e.g., cystic fibrosis, HIV) can cause dysglycemia or hyperglycaemia in the ranges found in diabetes. Many of these patients are classified as having type 2 diabetes but lack the typical 'metabolic' profile of type 2 diabetes.

Specific therapies should be used depending on the cause of the diabetes, with the most obvious one the exploration and elimination of the cause (e.g., curation of disease or stopping diabetogenic-drugs).

Specific advice for pilots and ATCOs

Same guidance for these specific forms of diabetes exists as for type 2 diabetes, where fitness to function as pilots or ATCOs will depend on the therapy rather than on the type of diabetes diagnosed (see advice on therapy). Only when insulin or agents that can cause hypoglycaemia (sulphonylurea) are introduced, does fitness to fly become an issue.

5. SCREENING FOR AND DIAGNOSIS OF COMPLICATIONS OF DIABETES

5.1 DIABETIC NEUROPATHY

One of the most prevalent forms of neuropathy worldwide is diabetic neuropathy, which displays a broad spectrum of clinical symptoms. A majority of those clinically diagnosed with this condition present a form known as distal symmetrical neuropathy, which follows a pattern of progression dictated by the length of nerve fibers, and primarily manifests through sensory and autonomic disturbances. Such patients may experience discomfort, structural changes in their feet, and disturbances in autonomous nervous functions. Some individuals with diabetes might also develop neuropathies that are focal or multifocal, also impacting the cranial nerves and the autonomous nervous system.[38]

This condition which has a lifetime prevalence of ca. 50% is the cause for more hospital admissions than all other complications from diabetes put together, and it is implicated in 50% to 75% of amputations that are not related to trauma.[39,40]

6.1.1 Pathophysiology

The exact processes that lead to this condition remain partially unknown. The presence of a systemic inflammatory state in individuals with diabetes mellitus seems to be a fundamental factor in the onset of diabetic neuropathy. It is widely agreed upon that the development of diabetic neuropathy involves a multitude of factors, including complex interplay among blood sugar control levels, length of time living with diabetes, age-induced nerve cell degeneration, and other elements such as blood pressure, lipid levels, and body weight.

Research findings suggest that high levels of blood sugar, harmful effects of glucose, and disrupted insulin signalling together with other risk elements trigger multiple biochemical pathways, influencing the metabolic activities within cells.[41,42]

6.1.2 Diagnostic tests and screening recommendations

Of the different types of diabetic neuropathy, the most extensively researched are distal symmetric polyneuropathy (DSPN) and diabetic autonomic neuropathies, especially cardiovascular autonomic neuropathy (CAN).[43]

6.1.2.1 Distal symmetric polyneuropathy (DSPN)

According to ADA's Standards of Care, for DSPN it is recommended that[44]:

- Starting from the diagnosis of type 2 diabetes and five years post-diagnosis for type 1 diabetes, all patients should be evaluated for diabetic peripheral neuropathy, with a follow-up assessment at least annually.
- The evaluation for distal symmetric polyneuropathy ought to involve a thorough history taking and examination of temperature or pinprick sensation (to assess small fiber function) as well as vibration sensation via a 128-Hz tuning fork (for large-fiber function). Annual 10-g monofilament tests should be conducted on all patients to identify those at risk of foot ulcers and amputations.
- In patients showing signs of microvascular complications, the presence of autonomic neuropathy symptoms and signs should be assessed.

To evaluate the function of small and large nerve fibers and protective sensation, the following clinical tests can be utilized:

1. Small-fiber function: pinprick and temperature sensation.
2. Large-fiber function: vibration perception and 10-g monofilament.
3. Protective sensation: 10-g monofilament.

The patient's medical history, coupled with screening scores and a neurological examination of the lower limbs for symptom and sign evaluation, could rule out other types or causes of peripheral neuropathies such as those related to alcohol, vasculitis, nutrition, drugs or toxins, and tarsal tunnel syndrome. This process also helps to pinpoint the distinctive traits of diabetic peripheral neuropathy (DPN).[44]

Electrophysiological testing or consulting a neurologist for a diagnosis is infrequently required, except in circumstances where clinical characteristics are not standard, the diagnosis is uncertain, or another underlying cause is suspected. Such unusual features that may necessitate referral include motor neuropathy outweighing sensory neuropathy, uneven distribution of symptoms and signs, and swift progression of the condition. In more complicated cases, when the common signs and symptoms are absent, or when numerous other co-existing health conditions can complicate the diagnosis, it might be necessary to conduct nerve conduction studies (NCS) and skin biopsies. These tests can help identify the presence of large or small fiber neuropathy.[43]

6.1.2.2 Autonomic neuropathy

People who have been diagnosed with type 1 diabetes for five or more years, and all those with type 2 diabetes, should undergo an annual evaluation for autonomic neuropathy. It's crucial to carefully explore the symptoms and signs of autonomic neuropathy during the patient's history and physical examination. Notable clinical indicators of diabetic autonomic neuropathy can include a persistently high heart rate at rest, a drop in blood pressure upon standing, delayed stomach emptying, constipation, diarrhoea, faecal incontinence, erectile dysfunction, neurogenic bladder, and sweat gland dysfunction leading to either excessive or insufficient sweating.

The screening process for signs of autonomic neuropathy includes questioning about symptoms like dizziness, light-headedness, or weakness when standing up, fainting, intolerance to physical activity, constipation, diarrhoea, difficulty in emptying the bladder, urinary incontinence, or changes in sweating. If symptoms are present, additional tests might be warranted depending on the specific organ involved.[44]

In the initial stages, cardiovascular autonomic neuropathy (CAN) might not show any symptoms and can only be identified by reduced heart rate variability during deep breathing. Severe CAN may be characterized by a resting heart rate exceeding 100 beats per minute and orthostatic hypotension, which is a drop in systolic or diastolic blood pressure by more than 20 mmHg or 10 mmHg, respectively, upon standing, without a corresponding increase in heart rate.[44]

For diagnosing gastroparesis, the most reliable method is the evaluation of gastric emptying via scintigraphy of digestible solids, taken every 15 minutes for 4 hours after eating or via the 13C octanoic acid breath test.
Those with diabetes who experience frequent urinary tract infections, pyelonephritis, incontinence, or a noticeable bladder should undergo further bladder function assessment.[44]

5.2 DIABETIC RETINOPATHY

Diabetic retinopathy, a microangiopathy affecting the retina, is a condition that almost all individuals with diabetes will eventually experience. The eye disease poses two significant threats to a patient's vision: diabetic macular oedema (DME) and proliferative diabetic retinopathy (PDR). [45]

While the incidence and the risk of progression of diabetic retinopathy have both declined over the past 30 years, from up to 90% to less than 50%, the persons with recently diagnosed type 1 or type 2 diabetes have a much lower risk of proliferative diabetic retinopathy, macular oedema, and visual impairment as compared with patients from earlier periods, this compilation remains the most common cause of acquired blindness among persons of working age in the industrialized world [45,46]

A Cochrane review found evidence that risk of progressing to PDR can be escalated by several factors. High levels of HbA1c, indicative of poor glucose control, can heighten the risk of PDR and its vision-jeopardizing complications. This underlines the significance of continuous and effective blood glucose management, no matter the current DR severity level. Other risks associated with progression to PDR include renal impairment in individuals with Type 1 or Type 2 diabetes, being diagnosed with diabetes mellitus at a younger age, elevated triglyceride levels, and larger retinal venular diameters in those with Type 1 diabetes. Furthermore, the more advanced the DR severity, the higher the risk of progressing to PDR. Therefore, early detection of the disease, along with effective management of the aforementioned systemic risk factors, is crucial in mitigating the risk of PDR and safeguarding vision.[47]

5.2.1 Pathophysiology

Diabetic retinopathy (DR) is a microvascular disease, predominantly caused by hyperglycaemia, leading to retinal damage. Initial signs involve blood vessel dilation and pericyte loss, which triggers structural changes, microaneurysm formation, and breakdown of the blood-retinal barrier, possibly resulting in capillary occlusion and retinal ischemia. This leads to upregulated VEGF and angiopoietins, promoting vascular permeability and endothelial cell proliferation.

Inflammation is pivotal in DR's progression, with leukostasis, an early indicator, contributing to the breakdown of the blood-retinal barrier and endothelial cell loss. In DR, adhesion molecules expression is increased, which fosters leukocyte-endothelium adhesion, leukostasis, and inflammation.

Additionally, elevated levels of chemokines and proinflammatory cytokines have been observed, correlating with DR severity. Retinal neurodegeneration, characterized by neuronal apoptosis, is an early DR event. High glucose levels induce mitochondrial dysfunction and oxidative stress, increasing cell apoptosis. Importantly, neurodegeneration may precede microvascular changes. [48]

5.2.2 Screening and diagnosis

The diagnostic evaluation methods of diabetic retinopathy have significantly advanced. They include the extensive use of optical coherence tomography to evaluate the thickness of the retina and the pathology within the retina, as well as wide-field fundus photography for the detection of microvascular lesions that may not present any clinical symptoms.[49]

5.2.2.1 The American Diabetes Association's recommendation on screening for diabetic retinopathy[44]:

- Adults with type 1 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist within 5 years after the onset of diabetes.

- Patients with type 2 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist at the time of the diabetes diagnosis
- If there is no evidence of retinopathy for one or more annual eye exams and glycemia is well controlled, then screening every 1–2 years may be considered. If any level of diabetic retinopathy is present, subsequent dilated retinal examinations should be repeated at least annually by an ophthalmologist or optometrist. If retinopathy is progressing or sight-threatening, then examinations will be required more frequently.
- Programs that use retinal photography (with remote reading or use of a validated assessment tool) to improve access to diabetic retinopathy screening can be appropriate screening strategies for diabetic retinopathy. Such programs need to provide pathways for timely referral for a comprehensive eye examination when indicated.
- Women with pre-existing type 1 or type 2 diabetes who are planning pregnancy or who are pregnant should be counselled on the risk of development and/or progression of diabetic retinopathy.
- Eye examinations should occur before pregnancy or in the first trimester in patients with pre-existing type 1 or type 2 diabetes, and then patients should be monitored every trimester and for 1 year postpartum as indicated by the degree of retinopathy.

If signs of diabetic retinopathy are detected during a screening, it is advised to immediately consult an ophthalmologist. Generally, patients with type 1 or type 2 diabetes who show minimal to no signs of retinopathy should have their eyes examined yearly. After one or more normal eye examinations, scheduling exams every 1–2 years may be an efficient use of resources. For individuals with well-managed type 2 diabetes, the likelihood of developing significant retinopathy within a 3-year period following a normal examination is minimal.

Nevertheless, the frequency of screenings should be tailored according to the presence of particular risk factors for the onset and escalation of retinopathy. If retinopathy is advancing or risk factors like poorly controlled hyperglycaemia, severe initial retinopathy, or diabetic macular oedema exist, examinations by the ophthalmologist will need to be conducted more regularly. [44,49]

A thorough assessment by an ophthalmologist will encompass dilated slit-lamp examination, which includes bio microscopy with a handheld lens (90 or 78 dioptre), indirect ophthalmoscopy, and, as needed, additional tests such as optical coherence tomography and fluorescein angiography.[49]

5.3 DIABETIC NEPHROPATHY

Roughly 20% to 40% of individuals with either type 1 or type 2 diabetes face the risk of diabetic kidney disease. This medical condition manifests with continuous high levels of albumin in urine (beyond 300 mg in a day or 300 mg for each gram of creatinine), an ongoing reduction in the GFR, elevated blood pressure, and a higher likelihood of heart-related complications and death. In typical cases of this kidney issue, an initial symptom is a slight rise in the albumin levels in the urine (known as microalbuminuria, falling between 30 and 300 mg in a day or 30 to 300 mg per gram of creatinine.[50]

6.3.1 Diagnosis of Diabetic Kidney Disease

According to the ADA's Standards of Care, diabetic kidney disease is often identified clinically by noting the existence of albumin in the urine and/or a diminished eGFR, especially when other clear reasons for kidney issues aren't evident. Common indicators of this ailment involve a lengthy history of diabetes, eye-related complications due to diabetes, albumin presence in the urine without noticeable blood, and a steady decrease in eGFR.

However, indications of this kidney problem can emerge at the initial diagnosis or even in the absence of eye-related complications in those with type 2 diabetes. It's not rare to see a lowered eGFR without the presence of albumin in both type 1 and type 2 diabetics, and such occurrences have been on the rise with the growing number of diabetes cases.[51]

6.3.1 Screening for Diabetic Kidney Disease: Albuminuria

Examining the urinary albumin-to-creatinine ratio (UACR) using a random urine sample is a straightforward method for albuminuria screening. Testing only for urine albumin, without considering urine creatinine, is cheaper but can be misleading due to variations from hydration. For effective patient screening, the basic dipstick tests need to be highly accurate and should be cross verified in a recognized lab. Hence, it's advisable to directly assess the UACR in a spot urine sample. [51–53]

Albuminuria levels are categorized as: normal (<30 mg/g creatinine), moderate (30–300 mg/g creatinine), and high (≥300 mg/g creatinine). Although UACR gives continuous data, even small variations in both regular and irregular ranges can indicate kidney and heart health implications. Given the natural fluctuation in urinary albumin output, at least two abnormal UACR readings from three samples within 3-6 months are needed to diagnose raised albuminuria. Factors like recent exercise, infections, extreme blood sugar, and specific physical conditions can affect UACR.[51–53]

6.3.2 Screening for Diabetic Kidney Disease: Evaluating eGFR

One of the most common ways to evaluate eGFR is derived from serum creatinine using the CKD-EPI formula. An eGFR consistently below 60 mL/min/1.73 m2 with a urinary albumin over 30 mg/g creatinine is deemed abnormal, with diagnostic criteria for those over 70 still under discussion. It's also recommended to use cystatin C in tandem with serum creatinine for more accurate clinical decision-making. [51,54]

5.4 CARDIOVASCULAR DISEASE

Cardiovascular, or macrovascular, disease, including coronary heart disease (CHD), cerebrovascular disease, and peripheral arterial disease, is estimated to be the main cause of health complications and mortality in people with diabetes.[55]
Compounding the issue, insights from the UK Prospective Diabetes Study (UKPDS) highlighted the importance of blood sugar targets for managing diabetes mellitus and delaying complications. However, the efficacy of the intervention on the macrovascular complications was not convincing.[56,57]

Nowadays, the newer drugs such as SGLT-2 inhibitors and GLP-1 agonists, have been proven in many studies to improve not only glycaemic control, but also reduce the rate of major adverse cardiovascular events. [58]
Although much studied, the relationship between diabetes mellitus and macrovascular complications is complex and multifactorial.[59] Nevertheless, the ADA on its Standards of Care provides some guidelines regarding screening for patients with diabetes mellitus who should undergo medical evaluation[55]:

6.4.1 Pathophysiology

Diabetes accelerates development of atherosclerosis and thus all types of cardiovascular disease, increasing risk two to four-fold. However, in particular people with type 2 diabetes will have an increased risk for cardiovascular disease, as not only hyperglycaemia is present, but type 2 diabetes is mostly embedded in a broader metabolic syndrome, with intraabdominal obesity, hypertension, abnormal lipid patterns etc.

6.4.2 Screening strategies based on the recommendations of the American Diabetes Association [55]

1. For Those experiencing typical or non-typical heart-related symptoms and for individuals with an irregular resting electrocardiogram (ECG): Begin with exercise ECG testing, with or without an accompanying echocardiography.

2. For adults with diabetes aged 40 and older, a coronary artery calcium measurement is advisable to gauge cardiovascular risk.

   Special considerations: If resting ECG irregularities, like left bundle branch block or ST-T changes, make exercise stress testing unsuitable for patients with diabetes, then pharmacologic stress echocardiography or nuclear imaging should be used.
   For those who need stress testing but can't exercise, pharmacologic stress echocardiography or nuclear imaging is recommended.

3. Screening asymptomatic individuals is not recommended.

Specific advice for pilots and ATCOs

Complications of diabetes will impact fitness to fly or function as pilot or ATCO in an important way, even more in some cases than type of diabetes or therapy. Screening for complications (in particular cardiovascular, eye and neurological) should be included in the medical screening.

In order to diagnose complications of diabetes (both macrovascular complications, i.e., cardiovascular diseases, and microvascular complications, i.e., diabetic retinopathy, neuropathy and nephropathy) at an early stage, the following recommendations are found in literature. However, once the complication has manifested itself, treatment follows the same principles as with persons without diabetes. Consequently, when assessing fitness to fly, it makes sense to manage macrovascular and microvascular complications much in the same way as this is done in the case of persons without diabetes.

This means to assess cardiovascular problems according to MED.B.010 rules, retinopathy according to MED.B.070 rules, renal problems according to MED.B035 rules and neuropathy according to MED.B065rules, independent of whether the reason for these problems diabetes is or not (for more comprehensive discussion of this topic see deliverable D2.1 in the EASA “Pilot and ATCO Aeromedical Fitness – Diabetes Mellitus” project).

6. GLUCOSE-LOWERING TREATMENT OPTIONS FOR PEOPLE LIVING WITH DIABETES: IMPLICATIONS FOR PILOTS AND ATCO – MAIN CONCLUSIONS

This section aims to provide a short overview of the diagnostic measures related to diabetes mellitus and its complications. It is important to accentuate that the evidence and recommendations should always be interpreted by an experienced physician in aviation medicine, internal medicine, or diabetology.

It should be clear that it is not the diagnosis of diabetes that will determine fitness to function as pilot or ATCO, but the quality of glycaemic control, the type of therapy and the presence of complications of the disease.

To date, pilots with diabetes mellitus who are treated with insulin or hypoglycaemia inducing agents like sulphonylurea are declared unfit to fly in most European countries but can fly commercial airlines in European countries such as the UK, Austria, and Ireland and in many countries outside Europe, when following strict monitoring protocols. Canada was the first country to permit carefully selected pilots with insulin-treated diabetes to fly commercial aircraft, starting in 2002. The UK joined in 2010 when the Civil Aviation Authority (CAA) assembled a team of experts to evaluate the scientific understanding of the issue. Subsequently, they formulated guidelines to ensure the safe flight of pilots on insulin therapy, culminating in the ARA.MED.330 protocol in 2012. This protocol, based on capillary blood glucose measurements, necessitates meticulous monitoring, comprehensive record-keeping, and systematic data gathering. It's important to note that current European Union regulations do not allow the issuance of Class 1 medical certificates (needed to validate a commercial pilot's license) or Class 2 medical certificates (required for a private pilot's license) to individuals with insulin-treated diabetes. However, these regulations do include provisions that allow for the consideration of emerging medical technologies, drugs, or methodologies to assess a pilot's fitness to fly.

No matter which type of diabetes, the diagnostic tests remain the same. Diagnosis of diabetes can be made on fasting glycemia, OGTT or using the more practical HbA1c, the latter allowing to consider the irregular lifestyle of pilots and ATCOs. Diagnosis cannot be made on capillary blood glucose measurements. The OGTT offers a dynamic relationship between how the body “reacts” to the glucose, considering the whole metabolic response, while the HbA1c provides an overall look at the glucose levels of the last couple of months, without much granularity and resolution.

Therefore, also when assessing pilots and ATCOs, it is important to have the choice between all available tests, because evidence has shown that the tests on their own are neither 100% sensitive nor specific. It is clear that lifestyle of pilots and ATCOs as well as AME and AeMC capabilities might, in some cases, give preference to one or the other test method; however, it should not be forgotten that all of them are used in clinical practice and therefore have their “raison d’être”.

Depending on the usual practice of the country where such measurements are taken, attention should be paid to the units (mmol/L or mg/dL). Pilots and ATCOs with diabetes mellitus traveling to territories with different systems should be familiar with their conversion and interchangeability.

Considering that prediabetes and type 2 diabetes are “silent conditions” and early interventions have been shown to reverse or slow down their progression, it’s important that a screening strategy is implemented, especially in people with risk factors. Screening is utterly important when it comes to the complications of diabetes mellitus. The longer a person has been diagnosed with diabetes mellitus, the higher the chances that they might develop complications. The severity and precipitance of complications are also affected by glycaemic control; poor glycaemic control is associated with higher complications.

While determining the risk of incapacitation from complications of diabetes mellitus is out of the scope of this review, it is worth noting that they would usually require a long time of having diabetes mellitus and further risk factors. Early screening and catered interventions in line with excellent diabetes management could delay such complications. However, once the complication has manifested itself, treatment follows the same principles as with persons without diabetes. Consequently, when assessing fitness to fly, it makes sense to manage macrovascular and microvascular complications much in the same way as this is done in the case of persons without diabetes. This means to assess cardiovascular problems according to MED.B.010 rules, retinopathy according to MED.B.070 rules, renal problems according to MED.B035 rules and neuropathy according to MED.B065rules, independent of whether the reason for these problems diabetes is or not (for more comprehensive discussion of this topic see deliverable D2.1 in the EASA “Pilot and ATCO Aeromedical Fitness – Diabetes Mellitus” project).

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