DIABETES MELLITUS

1. Introduction

Diabetes mellitus is a chronic endocrine disorder, characterized by hyperglycaemia resulting from absolute or relative insulin deficiency. There are a number of different causes of diabetes but by far the majority of cases are classified as either type 1 or type 2 diabetes.

The pathophysiology of type 1 diabetes derives from the autoimmune destruction of insulin-secreting pancreatic β-cells, resulting in insulin deficiency and subsequent hyperglycaemia. Type 1 diabetes accounts for about 10-15% of all diabetics. Type 2 diabetes is characterized by abnormal insulin secretion due to peripheral resistance and accounts for 85-90% of all persons with diabetes. While type 1 diabetes usually manifests itself in childhood or adolescence and type 2 diabetes at a later stage, clinical manifestation and progression vary considerably and some patients might not be clearly classified as having either type 1 or 2 initially. Type 1 diabetes may occur at any age and with late onset usually shows slower progression, and type 2 manifests itself more and more often earlier in life, even in childhood and adolescence, sometimes allowing for accurate diagnosis only over time.

In the uncontrolled state, both types of diabetes are characterized by increased hepatic glucose output and decreased glucose uptake in the muscles and adipose tissue. Patients with type 1 diabetes are at risk of severe lipolysis leading to diabetic ketoacidosis. The remaining insulin activity in type 2 diabetes usually inhibits lipolysis and ketone production such that these patients are less likely to develop ketoacidosis but are more likely to develop a hyperosmolar, non-ketotic state.

Worldwide, the incidence and prevalence of diabetes continues to rise due to both an increasing incidence of type 1 diabetes in children, and of type 2 diabetes due to lifestyle changes particularly in developing countries. In sports, diabetes is found at all levels of competition, and becomes a more common feature given the growing number of master athletes and because type 2 diabetes is occurring at increasingly younger ages. Also, given the markedly improved management possibilities of both types of diabetes more diabetic patients are able to compete at elite levels.

Physical exercise entails multiple physiological and psychological benefits for the diabetic patient. In type 1 diabetes, physical exercise plays a fundamental role in both physical and mental development. In type 2 diabetes, it is a major factor in improving insulin sensitivity and plasma glucose control. Accordingly, participation in sports should be encouraged and therapy optimized to enable these individuals to meet their full potential.

Athletes with diabetes may participate in almost all the competitive sports if certain precautions are taken. These measures must be individualized and continuously readjusted. For safe participation, diabetic patients should have a comprehensive pre-participation examination and thereafter regular medical examinations to optimize therapy and to screen for the development of long term complications. Caution might be advised for athletes with certain conditions as specified below (2. C; 8.).

2. Diagnosis

A. Medical History

Diabetes characteristically presents with a history of symptoms and signs associated with hyperglycaemia: polydipsia, polyuria, polyphagia (hyperglycaemic triad), weight loss, fatigue, skin and genital itching, dry mouth, stomatitis, visual disturbances, poor wound healing, recurrent infections, arrhythmia, confusion and (in men) erectile dysfunction and balanitis. It should be noted however that type 2 diabetes is often asymptomatic and identified through targeted screening programs.

A broad spectrum of vague symptoms including lethargy, nausea, blurred vision and recalcitrant fungal or bacterial infections may be the first early clues. Diabetes may also present as an acute hyperglycaemic crisis manifested by stupor, coma, or seizures.

B. Diagnostic criteria

Currently, four different diagnostic criteria are valid for diabetes:

- The HbA1C test is recommended for diagnosis of diabetes using a test method certified by the respective national authorities (point of care HbA1C tests are not suitable for the purpose of diagnosis), based on a threshold of ≥ 6.5%. The HbA1C test may be influenced by ethnicity, haemoglobinopathies and anaemias and becomes invalid in conditions with abnormal red cell turnover.

- Fasting plasma glucose (FPG) levels ≥7mmol/l (126 mg/dl). Fasting is defined as no calorie intake for the last eight hours.

- A 2-h plasma glucose value during an Oral Glucose Tolerance Test (OGTT) of ≥11.1 mmol/l (200mg/dl).

  The test should be performed according to the WHO instructions with an equivalent of 75 g anhydrous glucose dissolved in water.

- With the classic symptoms of hyperglycaemia or a hyperglycaemic crisis, a random plasma glucose ≥11.1 mmol/l (200mg/dl).

The HbA1C test is comparatively expensive and not yet readily available everywhere, therefore the FPG and OGTT criteria are likely to be still widely used particularly in developing regions of the world.

A positive test result for any of the three tests above should be repeated to exclude a laboratory error, unless history and clinical signs do not leave any doubt about the diagnosis. Preferably, the same test method should be used. In case of conflicting results from two different tests, the test being positive for diabetes should be repeated.

C. Relevant medical information

The primary evaluation of a newly diagnosed diabetic athlete must be comprehensive and include medical history, physical examination, appropriate laboratory analysis and in certain circumstances specialist assessment. The main objectives are to appropriately classify the type of diabetes and to detect the presence of any diabetes-related complications.

Evaluations of athletes with established diabetes should include interim medical history, duration of disease, family history, cardiovascular physical examination including blood pressure, retinal examination, foot assessment for neuropathy and peripheral vascular disease, HbA1c, lipid profile, renal function and urine analysis (a list of the components of a comprehensive assessment can be found in appendix 1).

Every diabetic athlete should be checked for existing diabetic complications before the start of an exercise program and pre-participation and regular pre-competition medical evaluations should be performed in diabetic athletes. Increased physical activity can precipitate a cardiac event including sudden death in those with underlying coronary artery disease, (uncontrolled) hypertension or cardiomyopathy which are more common in diabetics. Initial cardiac assessment should therefore include the cardiovascular risk factors such as hypertension, dyslipidaemia, and autonomic neuropathy. An exercise test may be part of the initial assessment.

In addition to noting maximal heart rate and blood pressure as well as ischaemic changes, exercise tolerance testing can identify anginal thresholds and asymptomatic ischaemia.

Athletes need to be further assessed for conditions such as severe peripheral neuropathy, pre-proliferative or proliferative retinopathy and macular oedema that represent a contraindication to types of exercise requiring

Valsalva maneuvers or those performed at high altitude. These conditions may also preclude vigorous exercise in some diabetics.

3. Medical best practice treatment

The primary goal of diabetes therapy is to keep plasma glucose levels as close to normal as possible without causing hypoglycaemia. Good control of plasma glucose helps to protect against the long term complications of diabetes.

For athletes with type 1 diabetes, insulin is always indicated and most athletes will require an intensive insulin regime with three or more injections of short acting insulin daily along with a once daily long acting insulin (basal bolus regime). Increasing numbers of individuals with type 1 diabetes are using insulin pumps which deliver a short acting insulin subcutaneously and continuously but at a rate that can be varied in a highly sophisticated way.

For athletes with type 2 diabetes, insulin is indicated when oral anti-hyperglycaemic medication is no longer sufficient to maintain glycaemic control. Type 2 diabetes is a progressive disease characterized by worsening hyperglycaemia requiring higher doses and additional medication to achieve treatment goals. Many athletes with type 2 diabetes will eventually need insulin and consideration should be given to early initiation of insulin therapy as a means of achieving and maintaining recommended levels of glycaemic control. Often, athletes with type 2 diabetes will require quite large doses of insulin to overcome the insulin resistance that is part of this condition.

A. Name of prohibited substance

Insulin is the most effective glucose-lowering agent and has no maximum dose. The main site of insulin action is the skeletal muscle. Insulin is available in a variety of short, intermediate and long acting preparations. There are also pre-mixed short and intermediate acting preparations in variable proportions. These insulins are administered using insulin syringes, pen devices or continuous subcutaneous insulin pumps.

While premixed insulins are sometimes used in people with type 1 diabetes, they are less useful in the diabetic athlete since they do not allow the same flexibility as intensive insulin regimens. Intensive insulin regimens consist of a long acting basal insulin together with prandial rapid acting insulin, or insulin pump therapy, and allow for dose adjustment of insulin around the time of and after exercise in athletes.

Insulin is also nowadays used at an earlier stage in the treatment of type 2 diabetes. According to current consensus statements which are applicable to adults above 18 years of age, insulin is among the medications in the first tier of

treatment algorithms. If lifestyle changes and maximal doses of metformin are insufficient to achieve treatment goals, either insulin or sulfonylureas should be considered as an additional medication. In type 2 diabetes, insulin is usually introduced as a once daily basal insulin, mostly given at bedtime. If still not sufficient to achieve treatment goals (usually HbA1c 7-7.5%), intensifying insulin injections is the therapy of choice. Metformin is usually maintained as an insulin sensitizer. For type 2 diabetics presenting with weight loss or other severe hyperglycaemic symptoms, initiation of insulin at the time of diagnosis may be indicated.

The above mentioned algorithm for type 2 diabetes cannot be applied to athletes under 18 years of age, as these present a special population requiring an individualized approach. The optimum treatment of type 2 diabetes in youth is not known. Oral anti-hyperglycaemic agents are not approved for children until age 18 in most countries, making lifestyle changes and insulin the mainstays of treatment (specific recommendations for youth diabetic athletes can be found in the references).

B. Route

Bolus subcutaneous injection or continuous subcutaneous infusion via an insulin pump device.

C. Dosage and Frequency

The dosage and frequency of insulin administration is dependent upon individual requirements and influenced by food intake, intensity and frequency of exercise sessions, pre-exercise plasma glucose levels etc. Regular self-monitoring of plasma glucose levels with glucose meters or sometimes with a Continuous Glucose Monitoring System (CGMS) provides an indication of immediate insulin need and is an indispensable part of all intensive insulin regimens.

The general aims of treatment are to keep plasma glucose concentration in an individually determined range and to prevent large deviations below 3 mmol/l or above 8-10 mmol/l. It is important that these goals are individualized. In practice it might be difficult for athletes to attain too strict goals. Very tight control increases the risk of hypoglycaemia during exercise. Insulin requirements in type 1 diabetes usually range between 0.5 and 1.0 U/kg/day, but may need to be reduced in athletes and lean subjects to around 0.2 to 0.6 U/kg/day. Athletes with type 2 diabetes often require higher doses (≥ 1.0 U/kg/day) to overcome insulin resistance.

The frequency of plasma glucose measurements carried out by the athlete themselves is dependent on the type of diabetes and the treatment regimen used.

Self-measurements are helpful in controlling plasma glucose levels and preventing extreme fluctuations. Athletes must have the relevant knowledge and understanding to be able to use this information appropriately and make meaningful adjustments to their regimes particularly in relation to exercise.

Consideration must be given to checking plasma glucose levels in the mornings, before, during and importantly after the end of an exercise session, and before and after meals. High risk activities (e.g. whenever access to carbohydrates is limited) may require very frequent glucose checks at 90, 30 and five minutes before their start. This is to try to avoid hypoglycaemia which would be extremely dangerous during these activities. Specialist assessment is indispensable before athletes with diabetes engage in high risk activities.

It is recommended either to reduce or even omit insulin doses in the period surrounding competitive or high intensity prolonged exercise, or to consume extra carbohydrates before, during or after the exercise session, or use a combination of both strategies. Frequent glucose monitoring and individualizing treatment regimens based on individual experience is key in the diabetic athlete.

Moderate- and high-intensity exercises have a contrasting effect on plasma glucose levels and require different management strategies to maintain euglycaemia. The response of plasma glucose levels to a combination of moderate- and high-intensity exercise, a pattern of physical activity referred to as intermittent high-intensity exercise (IHE) has received less research attention even though this type of exercise characterizes the activity patterns of most team and field sports. In very high intensity exercise (about 80% of VO_2 max) or when high intensity exercise follows a low intensity one, there is a tendency of plasma glucose to increase due to excessive circulating catecholamines necessitating postexercise short acting insulin. Prolonged exercise may also lead to decreased glucose counter regulation.

Athletes with diabetes who are treated with insulin and sulphonylurea drugs are at increased risk of hypoglycaemia during and after exercise due to the insulin-sensitizing effect of exercise. These athletes should be educated as to manage their diabetes around exercise to minimize the possibility of hypoglycaemic events occurring.

D. Recommended duration of treatment

The continuing need for insulin is self-evident in athletes with type 1 diabetes and is life-long (for TUE validity see 7). Given the progressive character of the disease, type 2 diabetic athletes that have been started on insulin for non-achievement of therapeutic goals with alternative medication will also most likely require this treatment life-long.

4. Other non-prohibited alternative treatments

Whilst the treatment of any diabetic athlete includes dietary control and education, insulin, for which there is no non-prohibited alternative, is the mainstay of therapeutic control in type 1 diabetes.

In type 2 diabetes, several classic and new anti-hyperglycaemic medications are available, with their choice being dependent on numerous individual factors. The glucose-lowering effectiveness of the different available monotherapy and combination therapy options depends on the duration of diabetes, baseline glycaemia, previous therapy and other factors. There is a growing variety of oral and injectible medications that complement the classic substances metformin and sulfonylureas (glinides, α-glycosidase inhibitors, thiazolidinediones, glucagon-like peptide-1 agonists, amylin agonists, dipeptidyl peptidase four inhibitors). However, current consensus statements do not support any of these new substances as tier 1 medications and consider only metformin and sulfonylureas as well validated initial medications (for algorithm, see 2. A above). Due to the progressive character of the disease, plasma glucose levels can often not be controlled adequately despite all these measures and insulin has to be introduced.

5. Consequences to health if treatment is withheld

Insulin treatment is essential to the survival of athletes with type 1 diabetes. If an athlete with type 1 diabetes omits or receives an insufficient dose of insulin, hyperglycaemia will develop and can progress to the life-threatening condition of diabetic ketoacidosis. Intense exercise may precipitate hyperglycaemia in athletes with diabetes.

Athletes who are treated with insulin but fail to achieve adequate plasma glucose control are at increased risk of long-term complications and end-organ damage including retinopathy, nephropathy, various neuropathies, diabetic foot disease and ischaemic heart disease.

An athlete with type 2 diabetes requiring insulin to maintain adequate plasma glucose control will also be exposed to the same potential increased risk of long term diabetes related complications should insulin treatment be withdrawn. There would also be a risk of metabolic decompensation which could ultimately lead to a hyperglycaemic crisis, but not ketoacidosis.

6. Treatment monitoring

Plasma glucose levels provide an indication of immediate insulin need, whilst the determination of glycosylated haemoglobin (Hb1Ac) provides an indication of plasma glucose control over the preceding 1 to 3 months.

Frequent self-monitoring of plasma glucose is paramount for any diabetic athlete including more frequent monitoring (and for longer periods following exercise) for those performing high-intensity or prolonged exercise. Any hypoglycaemic incidents should be documented and related to training intensity, plasma glucose levels prior to exercise, food and fluid intake, basal / bolus insulin dose, environmental conditions etc. and used to adjust future training, diet and / or treatment regimes accordingly.

The frequency of Hb1Ac testing depends on the individual, ranging from one to two times a year in stable diabetic athletes to every three months or even less in diabetic athletes with inadequate glycaemic control and those with very intense treatment regimes. The generally accepted goal for most diabetics is an Hb1Ac ≤7% with more or less stringent goals depending on the individual athletes, e.g. his or her inclination to hypoglycaemia.

The regular monitoring of diabetic athletes rests with the athlete themselves along with support from the primary care physician, diabetes nurse or diabetes specialist/endocrinologist.

7. TUE validity and recommended review process

In type 1 diabetes with clearly established primary diagnosis and in type 2 diabetes with proven need for insulin therapy, the recommended duration of a TUE for diabetes is 10 years with an annual review by a specialist physician.

Athletes are not required to regularly / annually submit the documentation from their medical specialist, but should be able to provide such documentation upon request by the ADO.

8. Any appropriate cautionary matters

In diabetes, there is a disturbed energy substrate use during exercise leading to either hypo- or hyperglycemia. With the modern diabetes therapies it is possible to achieve and maintain normoglycaemia in both types of diabetes but at the cost of a higher incidence of hypoglycemia, a potentially life-threatening condition, especially related to exercise. Prevention of hypoglycaemia is critical for the diabetic athlete as it increases the risk of falls, accidents and other (activity related) injuries. In type 1 diabetic athletes, exercise increases the risk of experiencing severe hypoglycaemia during exercise and for up to 31 hours of recovery afterwards. The sequelae of an exercise-induced severe hypoglycaemic reaction can be prevented with simple measures such as carrying glucose tablets or gel to be used in case of need. Ideally, the support staff of a diabetic athlete should be trained in the emergency treatment of hypoglycaemia.

When athletes with type 1 diabetes are deprived of insulin for more than 12 hours and are ketotic, exercise can worsen hyperglycemia and ketosis. Moderate to vigorous activity should therefore be avoided in the presence of ketosis. It is not necessary to postpone exercise based on hyperglycaemia only, provided the athlete feels well and urine and/or blood ketones are negative.

9. References

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Appendix 1

Components of comprehensive diabetes evaluation
(Source: American Diabetes Association. Standards of Medical Care in Diabetes – 2011. Diabetes Care. 2011 Jan;34 Suppl1:S11-S61)

Medical history
- Age and characteristics of onset of diabetes (e.g., DKA, asymptomatic laboratory finding)
- Eating patterns, physical activity habits, nutritional status, and weight history; growth and development in children and adolescents
- Diabetes education history
- Review of previous treatment regimens and response to therapy (A1C records)
- Current treatment of diabetes, including medications, meal plan, physical activity patterns, and results of glucose monitoring and patient's use of data
- DKA frequency, severity, and cause
- Hypoglycaemic episodes
    - Hypoglycaemia awareness
    - Any severe hypoglycaemia: frequency and cause
- History of diabetes-related complications
    - Microvascular: retinopathy, nephropathy, neuropathy (sensory, including history of foot lesions; autonomic, including sexual dysfunction and gastroparesis)
    - Macrovascular: CHD, cerebrovascular disease, PAD
    - Other: psychosocial problems,* dental disease*

Physical examination
- Height, weight, BMI
- Blood pressure determination, including orthostatic measurements when indicated
- Fundoscopic examination*
- Thyroid palpation
- Skin examination (for acanthosis nigricans and insulin injection sites)

- Comprehensive foot examination:
    - Inspection
    - Palpation of dorsalis pedis and posterior tibial pulses
    - Presence/absence of patellar and Achilles reflexes
    - Determination of proprioception, vibration, and monofilament sensation

Laboratory evaluation

● A1C, if results not available within past 2–3 months

If not performed/available within past year:

- Fasting lipid profile, including total, LDL, and HDL cholesterol and triglycerides
- Liver function tests
- Test for urine albumin excretion with spot urine albumin-to-creatinine ratio
- Serum creatinine and calculated GFR
- Thyroid-stimulating hormone in type 1 diabetes, dyslipidemia or women over age 50

Referrals

● Annual dilated eye exam
● Family planning for women of reproductive age
● Registered dietitian for MNT
● Diabetes self-management education
● Dental examination
● Mental health professional, if needed

*see appropriate referrals for these categories