ABC Article

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# Basic Management of Diabetes Mellitus: Practical guidelines

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## ABSTRACT

Diabetes mellitus is a major health problem associated with microvascular and macrovascular complications, leading to increased morbidity and mortality. It is rapidly growing worldwide with a huge economical and social burden. Although prevention and treatment of diabetes and its complications play a key role in reducing its morbidity and mortality, they require an integrated team approach at national and international levels. Early diagnosis, correct treatment, and effective follow-up are essential in any health care system to prevent complications of diabetes and ensure patients' well being.



## INTRODUCTION

Diabetes Mellitus (DM) is a rapidly growing chronic and multifactorial disease with a worldwide projection of 324 million diabetics by the year 2025 (1). In Africa, the prevalence of diabetes is expected to rise by 98%, from 13.6 million at 2003 to 26.9 million at 2025. A similar increase (97%) is expected in the Middle East region with an estimated prevalence of 35.9 million diabetics by 2025.

This emphasizes the health and economic threat diabetes poses in these countries as well as the importance of having recognized guidelines for the management of diabetes in order to prevent the

complications and ensure a normal quality of life to the patients. The prevalence of DM in Libya is not precisely known; although it has been estimated to be as high as 14.1% (prevalence of total glucose intolerance was 22.6%) (2). In this article, we briefly discuss the basic management of diabetes in adults directed mainly to medical students and junior colleagues. However, the different phases (and complications) of diabetes are beyond the scope of this review.

***Is it diabetes?*** Definite diagnostic criteria are crucial for identifying subjects with pre-diabetes [impaired fasting diabetes (IFG) and impaired glucose tolerance (IGT)] or diabetes. One casual measurement of blood glucose in a patient with symptoms and signs of diabetes, or two random postprandial measurements, are enough to make the diagnosis. However, oral glucose tolerance test (OGTT) is still the standard diagnostic and screening method for DM. The diagnostic criteria, (table 1) (3) uses plasma samples and whole blood samples. Whole blood samples, if used, will give ~ 11% lower values. One may also consider the differences between values obtained from capillary or venous samples, as venous samples have lower postprandial values.

***Meeting the patient:***

At diagnosis:

History: The most common symptoms are polyuria, polydipsia, and fatigue. The severity and duration of symptoms can help to differentiate type 1 from type 2 clinically, as the latter has a longer duration of onset (months) compared to type 1 (weeks). Strong family history and minimal weight loss are in favor of type 2. As ~ 20% of type 2 diabetics have a complication already at diagnosis, one should ask about symptoms of complications e.g. numbness and sensation loss in feet, claudicatio complaints, impaired vision (can also be caused by hyperglycemia), etc. Few patients present with infection at diagnosis or ketoacidosis.

Examination: Patients should be examined for signs of dehydration. Height, weight, BMI, rest pulse, and sitting blood pressure should be measured. Signs of complications should also be examined: these include blood pressures while lying down and standing up to test for orthostatic drop, foot pulses, vibration sense,

**Table 1: Diagnostic criteria of diabetes mellitus.**

| | NGT | IFG | IGT | DM |
|---|---|---|---|---|
| **Fasting pl- glucose** | < 110 mg/dl | 110 – 125 mg/dl | | ≥ 126 mg/dl |
| **2h pl-glucose (venous)** | < 140 mg/dl | | 140 – 199 mg/dl | ≥ 200 mg/dl |
| **2h pl-glucose (capillary)** | < 160 mg/dl | | 160 – 219 mg/dl | ≥ 220 mg/dl |
| **Fasting whole blood glucose** | < 100 mg/dl | 100 – 109 mg/dl | | ≥ 110 mg/dl |
| **2h whole blood glucose (venous)** | < 120 mg/dl | | 120 – 179 mg/dl | ≥ 180 mg/dl |
| **2h whole blood glucose (capillary)** | < 140 mg/dl | | 140 – 199 mg/dl | ≥ 200 mg/dl |

*NGT=normal glucose tolerance, IFG=impaired fasting glucose, IGT=impaired glucose tolerance, 2h = 2 hours (postprandial glucose), Pl=plasma.*

touch sense, and reflexes in lower extremities as well as fundal examination (by ophthalmologist).

***Laboratory investigations:***

Plasma glucose to confirm diagnosis (table 1).

Urine examination for ketonuria in type 1. If the test is positive, metabolic acidosis should be excluded.

C-peptide: Normal or high value indicates type 2, while low or immeasurable value indicates insulin deficiency (e.g. type 1).

Antibodies: e.g. GAD65Ab (glutamic acid decarboxylase-65 antibody) and ICA-ab (islet cell antibody), their presence indicates autoimmunity as in type 1.
HbA1c, serum creatinin, serum lipids (total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides) and urinary albumin.

***Annual follow up:***

History: Ask for symptoms of hyperglycemia or hypoglycemia, blood glucose values from patients self controls, symptoms of complications, and actual treatment and doses. Weight loss in uncontrolled diabetic may indicate the need for insulin treatment.

Examination: the patient should be examined for BMI, rest pulse, blood pressure (lying and standing), and signs of complications. Fundal examination by an ophthalmologist must be performed annually for patients with type 1, and biannually for patients with type 2. When retinopathy changes are detected, examination is repeated more often in accordance with an ophthalmologist's recommendations.

Laboratory investigations: HbA1c (4 times/yr), serum creatinin, serum lipids, and urinary albumin.



HbA1c (4 times/yr), serum creatinin, serum lipids, and urinary albumin.

ECG: for all patients with type 2 diabetes and patients with type 1 diabetes at 40 years or older with at least one cardiovascular risk factor (hypertension, hyperlipidemia, albuminuria, smoking or ischemic heart disease).

***Current treatment of diabetes mellitus:***

Patient education: in all types of diabetes.

Diet treatment: in all types of diabetes.

Physical training: in all types of diabetes. It reduces weight, central obesity, and blood lipids while improving insulin sensitivity, thus improving plasma glucose.

Stop smoking: in all types of diabetes.

Acetylsalicylic acid: 75-160mg daily should be considered for all patients with type 2 DM, and patients with type 1 DM older than 40 years with at least one cardiovascular risk factor.



***Oral antidiabetics:***

Insulin secretion stimulators:
Sulphonylureas: An old class, less often used nowadays due to risk of hypoglycemia. They are long acting drugs with less effect on post-prandial hyperglycemia. Examples of this class: Glibenclamide (Daonil), Glipizide (Mindiab) and Glimepiride (Amaryl).

Metiglinides: A relatively new group of drugs. They are preferred over sulphonylureas, as they have shorter duration of action, pose less risk for hypoglycemia, and are more effective on post-prandial hyperglycemia, even when pre-prandial glucose values are acceptable. They are given before meals. Examples of this class: Repaglinide (Novonorm) and Nateglinide (Starlix).

***Insulin sensitizers:***

Biguanides: Metformin is the only drug in this group. It is widely used and considered first line treatment in DM type 2. Gastrointestinal side effects are common but avoidable by slow up titration of doses.

Thiazolidinediones (Glitazones): Examples of this class: Rosiglitazone (Avandia) and Pioglitazone (Actos). Side effects are weight gain and fluid retention. Maculoedema has also been reported.

***α glucosidase inhibitor:***

Acarbose (Glucobay): It has limited use due to gastrointestinal side effects.

Insulin:

Short acting human insulin: its use is mostly limited now to acute situations where intravenous insulin infusion or intramuscular injections are needed e.g. Diabetic ketoacidosis or hyperosmolar non-ketotic coma. Example of

this class: Actrapid.

Rapid acting insulin analogues: the insulins of choice at meal time, they have less hypoglycemic risk and better effect on post-prandial hyperglycemia. Examples of this class: insulin Aspart (Novorapid) and insulin Lispro (Humalog).

Intermediate acting insulins: are used as base insulin. Examples of this class: Human insulin: Insulatard and Humulin NPH, insulin analog: insulin Detemir (Levemir).

Long acting: insulin analog: an example of this class is insulin Glargine (Lantus). It has less risk for hypoglycemia and more stable plasma distribution with almost peakless levels after injections.

Mixed insulins: insulin analogues, examples are Novomix 30, Humalog mix 25, and Humalog mix 50. The previously widely used mixed human insulins (e.g. insulin Mixtard) are rarely used since the introduction of mixed insulin analogues.

Insulin inhalers: an example of this class is Exubera, human insulin. It s approved in Europe and USA, and expected to be available for clinical use in Sweden in autumn 2006. It is a rapid acting insulin to be given at meal times, for type 1 and 2 diabetics. The use will probably be initially restricted to patients with type 2 diabetes who are badly controlled on all possible standard injection therapies. However, it should be used with caution until enough experience and more studies are available on this kind of insulin therapy.

Future classes:

Glucagon like peptide 1 (GLP-1) analogs, (example: Liraglutide, Novonordisk) and Dipeptidyl peptidase 4 (DPP-4) inhibitors (example: Sitagliptin, Merck and Vildagliptin, Novartis). They act mainly by stimulating insulin secretion.



***Drug treatment strategy:***

Type 1 diabetes (absolute insulin deficiency):

**Multiple insulin injections:** Rapid acting insulin (Novorapid/ Humalog) at meal time and Lantus once at night as base insulin is the mostly used regimen. Lantus can also be given at any time during the day e.g. morning, at lunch, or in the evening. As alternatives to Lantus, Insulatard or Detemir can be used once or

twice daily. Regular blood sugar self controls are strongly recommended. A whole day profile (at breakfast, lunch, evenings meal and bedtime) 1-2 times/week is preferred.

In cases with insulin deficiency in elderly patients [DM type 1, latent autoimmune diabetes in adults (LADA) or secondary diabetes to pancreas diseases], a more simple insulin regimen can be used instead, e.g. 2 doses of mixed insulin daily.

**Insulin pump:** Continuous subcutaneous insulin infusion (CSII) can be considered in insulin dependent patients with good compliance and sufficient education.



**TYPE 2 DIABETES (RELATIVELY PRESERVED INSULIN SECRETION):**

**Diet and physical training:** is the first line treatment. Regular blood sugar self controls should be used. If blood glucose is still not controlled, add treatment in next step.

**Oral treatment:** Patient with overweight: Metformin as initial therapy can be used in increasing dose to avoid side effects (alternative glitazone e.g. Avandia or Actos). If blood glucose is still not well controlled, add Novonorm or Starlix. Patients with normal BMI: Novonorm or Starlix can be used initially. They can be combined with Metformin or glitazone.
If still not controlled:

**Insulin treatment:** Base insulin can be added to ongoing oral treatment, ex: Lantus or Insulatard once daily. Glitazone treatment is contraindicated in combination with insulin therapy. Mixed insulin, ex: Novomix 30 or Humalog mix 25, can be given before breakfast and dinner. Patient can continue on Metformin while insulin secretion stimulators are usually (but not always) discontinued. In severe insulin resistant cases requiring large insulin doses, multiple insulin injections are used as those in type 1 diabetes, usually in combination with Metformin.

**Goals and limits of treatment:** Lowering blood glucose and HbA1c is crucial to reduce the risk for vascular complications in patients with type 1 (4, 5) and type 2 diabetes (6, 7). The goals of treatment summarized in table 2 are according to recommendations of the American Diabetes Association (8) and national guidelines in Sweden (9). The aims of these guidelines are to

prevent the complications and ensure the well-being of patients. These goals, especially blood glucose and HbA1c, should be individualized depending on patient's age, type of diabetes, presence of complications, multiorgan and psychiatric disease. It should not take a long time (in type 2, insulin therapy should be reached within 5 years after diagnosis) to reduce the HbA1c to the recommended level. The lowest possible HbA1c that can be reached, without serious hypoglycemic events or side effects is probably the best definition of goal HbA1c in term of individualization the goal. In elderly patients, tight control of blood glucose may not be recommended due to high risk of hypoglycemia. Other parameters are as important as HbA1c regarding the risk for vascular complications. Patients with well controlled blood pressure have lower risk for myocardial infarction and stroke. A 1% reduction in serum LDL-cholesterol reduces the risk for total mortality by 12%.

**Table 2: The goal levels of diabetes related parameters during treatment**

| Measure | Recommended level |
|---|---|
| HbA1c | < 7.0% |
| Fasting P-glucose | 90-130 mg/dl |
| PP P-glucose | 90-162 mg/dl (<180 mg/dl) |
| Blood pressure | < 130/80 mmHg |
| Serum Total-Cholesterol | < 200 mg/dl |
| Serum LDL-Cholesterol | < 100 mg/dl |
| Serum HDL-cholesterol | > 40 mg/dl |
| Serum Triglycerides | < 150 mg/dl |
| BMI | < 25 kg/m² (male), < 24 kg/m² (female) |

There is an ongoing discussion in Sweden in order to lower the level of treatment goals: HbA1c 6.8% in type 1, HbA1c 5.9-6.8% in type 2 (lower HbA1c in type 2 due to less risk for hypoglycemia), serum total cholesterol <170 mg/dl and blood pressure in patients with nephropathy <120/70 mmHg. The reason for this additional tightening of treatment goals is the occurrence of complications at low HbA1c levels (>5.9%).

To apply these goals is practi-

cally difficult, but the patient is ultimately the beneficiary. Again, individualization of the treatment is of extreme importance in the management of patients with diabetes. The self-control of blood glucose by patients and education of both patients and diabetes health care teams are the most important steps to be considered by colleagues and authorities to improve the diabetes care.

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