Diabetes Mellitus: Diagnosis and Management Guidelines

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Abstract: Diabetes mellitus is a metabolic disorder of carbohydrate metabolism, with under utilization of glucose, leading to hyperglycaemia. Type 2 diabetes is in epidemic proportions and achieving specific glycemic goals can substantially reduce morbidity. Effective treatment of hyperglycaemia is the center stage in the treatment of diabetes. Therapies directed at other coincident features, such as dyslipidemia, hypertension, hypercoagulability, obesity, and insulin resistance, have also been a major focus of research and therapy. The present article focuses on the diagnosis and management strategies of this complex metabolic disorder.

INTRODUCTION

Diabetes mellitus is a group of metabolic disorders of carbohydrate metabolism in which glucose is underutilized and overproduced, causing hyperglycaemia. Diabetes mellitus is a complex, chronic illness which requires continuous medical care. There are multifactorial risk reduction strategies which act beyond glycaemic control. Prevention of acute complications and reduction of the risk of long-term complications can be done by patient self-management education and support. It is a well recognized fact that the type 2 diabetes is in epidemic proportions and achieving specific glycemic goals can substantially reduce morbidity. Thus effective treatment of hyperglycaemia has attained a top priority. Center stage in the treatment of diabetes, is management of hyperglycaemia, the hallmark metabolic abnormality associated with type 2 diabetes, therapies directed at other coincident features, such as dyslipidemia, hypertension, hypercoagulability, obesity, and insulin resistance, have also been a major focus of research and therapy. Maintaining glycemic levels as close to the nondiabetic range as possible has been demonstrated to have a powerful beneficial effect on diabetes-specific microvascular complications, including retinopathy, nephropathy, and neuropathy, in the setting of type 1 diabetes.

DIAGNOSIS OF DIABETES

Diabetes is diagnosed based on plasma glucose criteria, either the fasting plasma glucose (FPG) or the 2-hour plasma glucose (2-h PG) value after a 75-g oral glucose tolerance test (OGTT). Recently, an International Expert Committee, which comprised members appointed by the American Diabetes Association (ADA), the European Association for the Study of Diabetes, and the IDF, added the A1C (threshold > 6.5%) as a third option to diagnose diabetes. The World Health Organization (WHO), American Diabetic Association (ADA) and the International Diabetes Federation (IDF) have recommended an FPG value ≥ 7.0mmol/L (126 mg/dL); a 2-h postload glucose concentration ≥ 11.1 mmol/L (200 mg/dL) during an OGTT; or symptoms of diabetes and a casual (i.e., regardless of the time of the preceding meal) plasma glucose concentration ≥ 11.1 mmol/L (200 mg/dL). If any one of these criteria is met, confirmation by repeat testing on a subsequent day is necessary to establish the diagnosis [note that repeat testing is not required for patients who have unequivocal hyperglycaemia, i.e., ≥ 11.1 mmol/L (200 mg/dL) with symptoms consistent with hyperglycaemia].

PREDIABETES

In 1997 and 2003, a group of individuals whose glucose levels did not meet the criteria for diabetes, but were too high to be considered normal, were recognized by the Expert Committee on Diagnosis and Classifications of Diabetes Mellitus. These persons were diagnosed to be having prediabetes. Prediabetes was defined as impaired fasting glucose (IFG) (FPG levels 100–125mg/dL [5.6–6.9 mmol/L]), or impaired glucose tolerance (IGT) (2-h PG OGTT values of 140–199 mg/dL [7.8–11.0 mmol/L]). (Table 2)

SCREENING OF DIABETES

Screening of diabetes is done in an asymptomatic individual if there is an increased risk of development of Diabetes or after the age of 45 years. The individuals at an increased risk of diabetes are shown in Table 3. MANAGEMENT OF DIABETES MELLITUS

The goals of therapy for type 1 or type 2 DM are:
(1) Eliminate symptoms related to hyperglycemia,
(2) Reduce or eliminate the long-term microvascular and macrovascular complications of DM

Figure 1: Approach to Diabetic patient – Adopted from American Diabetic Association

(3) Allow the patient to achieve as normal a lifestyle as possible

GLYCAEMIC GOALS FOR DM
The glycaemic goals for patients with Diabetes are11
1. A1C < 7.0%
2. Preprandial capillary plasma glucose 70–130 mg/dL (3.9–7.2 mmol/L)
3. Peak postprandial capillary plasma glucose < 180 mg/dL (10.0 mmol/L)

Goals should be individualized based on: duration of diabetes, age/life expectancy, co-morbid conditions, known cardiovascular disease (CVD) or advanced microvascular complications, hypoglycemia unawareness, individual patient considerations, more or less stringent glycaemic goals may be appropriate for individual patients12. (Figure 1)

More stringent HbA1c targets (e.g., 6.0–6.5%) might be considered in selected patients (with short disease duration, long life expectancy, no significant CVD) if this can be achieved without significant hypoglycemia or other adverse effects of treatment12,13. Conversely, less stringent HbA1c goals e.g., 7.5–8.0% or even slightly higher are appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced complications, extensive co-morbid conditions14.

BLOOD PRESSURE AND LIPID TARGETS IN PATIENTS WITH DM
Blood pressure target in these patient is <130/80 mm Hg. The low-density lipoprotein cholesterol should be <2.6 mmol/L (100 mg/dL). High-density lipoprotein cholesterol should be >1 mmol/L (40 mg/dL) in men >1.3 mmol/L (50 mg/dL) in women and triglycerides should be <1.7 mmol/L (150 mg/dL).

EXERCISE
For individuals with type 1 or type 2 DM, exercise is also useful for lowering plasma glucose (during and following exercise) and increasing insulin sensitivity. In patients with diabetes, moderate aerobic physical activity of 150 min/week (distributed over at least 3 days) is recommended by ADA. The exercise regimen should also include resistance training15.

PHARMACOLOGIC THERAPY
Pharmacological therapy is aimed at maintaining the glycaemia and reducing the long-term complications of Diabetes. Drug classes used for the treatment of type 2 diabetes include the following: (Table 4)

1. Insulin sensitizers: (a) Biguanides; (b)Thiazolidinediones (TZDs); (2) Insulin secretagogues: (a) Sulfonylureas; (b) Meglitinide derivatives; (3) Alpha-glucosidase inhibitors; (4) Glucagon-like peptide–1 (GLP-1) agonists; (5) Dipeptidyl peptidase IV (DPP-4) inhibitors; (6) Selective sodium-glucose transporter-2 (SGLT-2) inhibitors (7) Insulin; (8) Amylinomimetics

INSULIN SENSITIZERS
1. Biguanides
Biguanides decreases hepatic gluconeogenesis. It also decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. It is contraindicated in patients with Congestive Heart Failure (CHF), renal or hepatic dysfunction, or binge alcoholism. They should be held shortly before surgical procedures and before radiologic studies involving intravenous contrast. The initial starting dose of metformin is 500 mg once or twice a day can be increased to 1000 mg bid13–19.

2. Thiazolidinediones (TZDs)
Thiazolidinediones reduce insulin resistance by binding to the Peroxisome proliferator activatedreceptor (PPAR) gamma. The therapeutic range for pioglitazone is 15–45 mg/d. These agents are contraindicated in patients with liver disease or CHF (class III or IV). These agents are associated
with increased risk of fractures, and rarely may experience a worsening of diabetic macular edema. The safety of thiazolidinediones in pregnancy is not established17–19.

Insulin secretagogues: Insulin secretagogues stimulate insulin secretion by interacting with the ATP-sensitive potassium channel on the beta cell17–20.

1. Sulfonylureas
They reduce both fasting and postprandial glucose and should be initiated at low doses and increased at 1- to 2-week intervals based on self-monitoring of blood glucose (SMBG) commonly used drugs are glimeperide (dose range: 1-8 mg), gliclazide (dose range: 40-240 mg) and glipizide (dose range: 5-20 mg).

2. Meglitinide derivatives
Repaglinide (dose range: 0.5-16 mg) and nateglinide (dose range: 180-360 mg) are not sulfonylureas but also interact with the ATP-sensitive potassium channel. Because of their short half-life, these agents are given with each meal or immediately before to reduce meal-related glucose excursions.

3. Alpha-glucosidase inhibitors
Alpha-glucosidase inhibitors acarbose (dose range: 25-100 mg per meal), miglitol (dose range: 25-50 mg per meal) and voglibose (dose range: 0.1-0.3 mg per meal), reduce postprandial hyperglycemia by delaying glucose absorption. These agents should not be used in individuals with inflammatory bowel disease, gastroparesis, or a serum creatinine >177 mol/L (2 mg/dL)17–20.

4. Glucagon like peptide–1 (GLP-1) agonists
GLP-1 is produced in the L cells of small intestine and stimulates insulin secretion and inhibits glucagon secretion in a glucose-dependent manner. Dosing is twice daily by subcutaneous injection. Starting dose of exanatide is 5 µg. If this dose is tolerated, titrate after 1 month to 10 µg. Due to its delaying effects on gastric emptying, the major side effect is GI complaints such as nausea, vomiting, and diarrhea17–20.

Dipeptidyl peptidase IV (DPP-4) inhibitors
Dipeptidyl peptidase 4 (DPP 4) is a cell membrane protein that rapidly degrades GLP-1 and glucose-dependent insulinotropic polypeptide. Suppression of DPP 4 leads to higher levels of insulin secretion and suppression of glucagon secretion in a glucose-dependent manner. The glitazins in common use are- sitagliptin, vildagliptin, saxagliptin and lixisnaptin.

Dosing of sitagliptin is 100 mg orally once daily, saxagliptin is 2.5 or 5 mg orally once daily, lixisnaptin is 5 mg orally once daily and vildagliptin is 50 mg twice daily. Liniaptin does not require dose adjustments with renal failure17–19.

Insulin
Insulin is the oldest therapy available for diabetes. It was discovered in 1921, and clinical testing in humans started in 1922. To this date it remains the most effective method of reducing hyperglycemia. There is no upper limit in dosing for therapeutic effect. Hypoglycaemia is the major side effect. Various forms of insulin are shown in Table 516–19.

<table>
<thead>
<tr>
<th>Table 4: Various drug classes used in treatment of Diabetes</th>
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<tbody>
<tr>
<td>Class</td>
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<tr>
<td>-------</td>
</tr>
<tr>
<td>biguanides</td>
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<tr>
<td>thiazolidinediones</td>
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<tr>
<td>meglitinides</td>
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<tr>
<td>alpha-glucosidase inhibitors</td>
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<tr>
<td>sulfonylureas</td>
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<tr>
<td>DPP-4 inhibitors</td>
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<tr>
<td>GLP-1 receptor agonists</td>
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<tr>
<td>basal insulin</td>
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Table 5: Insulin Preparations

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<tr>
<td>Preparation</td>
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<tr>
<td>NPH</td>
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<tr>
<td>Lente</td>
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<tr>
<td>Isophane</td>
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<td>Detemir</td>
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<td>Glargine</td>
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APPENDIX TO GLYCAEMIA MANAGEMENT

The algorithm for glycaemia management recommend an HbA1c of 6.5% or lower for healthy patients without concurrent illness and at low risk for hypoglycemia but individualized target HbA1c values greater than 6.5% for patients with concurrent illness and those who are at risk for hypoglycemia. Lifestyle modification, including weight loss, is a component of all treatments. Metformin is the preferred initial agent for monotherapy and is a standard part of combination treatments.

Dual drug therapy
If the glycaemic goal is not achieved or sustained within 2-3 months, another medication should be added. The choice of addition of second drug is also individualized as per the patient characteristic and involvement (eg, a DPP-4 inhibitor if both postprandial and fasting glucose levels are elevated; a GLP-1 agonist if postprandial glucose levels are strongly elevated; a TZD if the patient has metabolic syndrome and/ or nonalcoholic fatty liver disease). Before adding a second agent for a patient who is taking an insulin secretagogue, the clinician should warn the patient about the possibility of hypoglycemia.

Triple drug therapy
If 2 drugs proves unsuccessful after 2-3 months, the next step is triple therapy. The third drug may be an oral agent from a third class of antidiabetic drugs or basal insulin (typically at bedtime).
Insulin therapy

In case of type 1 DM the only available therapy is insulin however in type 2 DM the patients who are not able to achieve glycaemic targets by oral agents, the insulin therapy should be instituted. Sulphonylureas should preferably be omitted from the treatment and patient should be subjected to insulin therapy. All insulin injections should preferably be administered in the abdomen, although they can also be given in the thigh, hip, or buttock regions.

Multiple daily dosing

Multiple daily dosing of insulin gives the patient the greatest flexibility. Long-acting insulin (eg, glargine, detemir or NPH) is generally given once daily as the basal insulin and rapid-acting insulin (eg, aspart, glulisine, lispro or regular) is administered just before each meal.

Twice daily premixed insulin

Twice daily injections of premix insulin are given before breakfast and before dinner. This regimen is suitable for those patients who are reluctant for multiple injections.

Continuous subcutaneous insulin infusion (CSII) or insulin pump therapy

The ideal CSII candidate is a patient with type 1 diabetes mellitus or intensively managed type 2 diabetes mellitus who is currently performing 4 or more insulin injections and 4 or more self-monitored blood glucose measurements daily; is motivated to achieve optimal blood glucose control; and is willing and able to carry out the tasks that are required to use this complex and time-consuming therapy safely and effectively; and is willing to maintain frequent contact with their health care team.

EMERGING THERAPIES

Whole pancreas transplantation (performed concomitantly with a renal transplant) may normalize glucose tolerance and is an important therapeutic option in type 1 DM with ESRD. Pancreatic islet transplantation had a limitation of pancreatic islet supply and graft survival and remains an area of clinical investigation. Other newer therapies under investigation are outlined in table 6.

Bariatric surgery for markedly obese individuals with type 2 diabetes has shown considerable promise. The ADA clinical guidelines state that bariatric surgery should be considered in individuals with DM and a BMI >35 kg/m².

REFERENCES


Table 6: Novel Compounds Currently in Clinical Development for the Treatment of Hyperglycemia in Patients with T2DM

<table>
<thead>
<tr>
<th>Drug Category</th>
<th>Mechanism of Action</th>
<th>Potential Advantages</th>
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<tbody>
<tr>
<td>Insulin analogues</td>
<td>Unaltered, modifications of solute channels in pancreatic β-cells may enhance glucose-stimulated insulin secretion</td>
<td>Improved glucose control and cardiac microvascular flow</td>
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<tr>
<td>CNOS</td>
<td>Release of the channel to insulin in the central nervous system *Significantly affects appetite regulation</td>
<td></td>
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<tr>
<td>diazepine-PPAR</td>
<td>Variable activation of the nuclear transcription factor PPARγ in addition to PPARα and PPARβ</td>
<td></td>
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<tr>
<td>Selective PPAR-γ modulators</td>
<td>Partial and selective activation of the nuclear transcription factor PPARγ</td>
<td></td>
</tr>
<tr>
<td>Glucokinase activator</td>
<td>Stimulation of the key enzyme in liver to increase hepatic glucose metabolism and in pancreatic ß-cells to increase insulin secretion</td>
<td>Complementary mechanisms of action</td>
</tr>
<tr>
<td>GLP-1 receptor agonists</td>
<td>Inhibition of the enzyme that regulates embryonic development in liver and adipose tissue, thereby improving insulin sensitivity</td>
<td></td>
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<tr>
<td>Biotinylated insulin</td>
<td>Inhibition of the enzyme that regulates fibrogenic pathways</td>
<td></td>
</tr>
<tr>
<td>PPAR-Î± agonists</td>
<td>Inhibition of a protein in muscle and liver that downregulates insulin signaling, thereby improving insulin sensitivity</td>
<td></td>
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<tr>
<td>Acetyl-CoA carboxylase</td>
<td>Reduces in the mazloz/CoA production, with subsequent increase in fatty acid oxidation in liver and adipose tissue</td>
<td></td>
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<tr>
<td>Glucagon receptor antagonists</td>
<td>Blockade of the effect of glucagon in liver to stimulate hepatic glucose production</td>
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TELEMEDICINE

Telemedicine is an innovative, currently used to strengthen continued healthcare in the rural communities. Lack of computer savvy personnel, non-availability of advance equipment and uniform guidelines are some grey areas.

Telemedicine is the use of electronic information and communication technologies to provide and support healthcare in remote areas. For more than 3 decades clinicians, health service researchers and others have been investigating that use of advanced telecommunication and information technologies (IT) for improving healthcare. Telemedicine has variety of application in patient care, health education research, administration and public health. Commonest of all is use of emergency number call by ordinary telephone. Other applications like telesurgery, home monitoring of patients are yet to get attention and routine application in day-to-day practice.

Early application of Telemedicine was often focused on remote populations scattered across mountainous areas, islands, open plains and arctic regions where doctors were not easily reached, but recently as the cost of communication and IT has dropped there is an wave of interest propelled in the era of superspecialisation, telemedicine offers a mechanism for centralising specialist and supporting primary care physician at remote places. Proper use of telemedicine will emphasis doctor to doctor communication and fill up the gap of non-availability of specialist in remote unaccessible areas. It will improve advanced emergency help to the patients and will provide more room for evidence-based medical practice. However, some medicolegal and ethical issues will prop up and will require a plausible solutions.