GUIDELINES FOR CARE OF TYPE 2 DIABETES MELLITUS IN BANGLADESH

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28 February 2003

Published by
BIRDEM Clinical Research Group
Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders
Ibrahim Memorial Diabetes Centre
122 Kazi Nazrul Islam Avenue
Shahbagh, Dhaka-1000
Bangladesh

Introduction

About 90% - 95% of all diabetes patients of Bangladesh belong to Type 2 diabetes. Onset is often insidious and asymptomatic.

Type 2 diabetes is considered as a compound of complex metabolic syndrome. It can lead to both micro and macrovascular complications of DM.

It is VITAL to consider not only the abnormalities of glucose metabolism but also other associated health hazards e.g. obesity, hyperlipidaemia, hypertension, retinopathy, nephropathy, neuropathy, foot ulcer etc.

It is important to emphasize that the patient himself is his doctor. Physicians, nurses and educators can act only as his guide. Therefore, self-monitoring is important for both treatment and assessment of diabetes control.

Education of the patient and their families improves compliance, quality of life and safety of therapy.

Objectives and priorities of treatment must be tailored according to the individual's clinical context. Aggressive treatment in the elderly should be avoided.

The Primary Objectives of Management are:

Relief of symptoms,
Improved of quality of life,
Sense of wellbeing,
Prevention or delay of acute and/or chronic complications,
Achieve normal/near normal metabolic control,
Reduction of mortality and morbidity,
Treatment of associated disorders,
Good pregnancy outcome,
Assurance for availability of insulin, syringes, OHA and diagnostic test strips for assessing control.
Rehabilitation of diabetes, when necessary.

Whom to screen

1. Persons above 40 years age
2. Obese individuals
3. Persons with family history of diabetes mellitus
4. Those with classical symptoms of diabetes mellitus
5. Previous GDM
6. History of hyperlipidemia, hypertension, IHD, hyperuricaemia.

Diagnostic Criteria of DM (Non-Pregnant Adults)

A person can be diagnosed as a diabetic, if any two of the following criteria are present –

1. More than one characteristic symptom and sign of DM.
2. Fasting venous plasma glucose ≥7.0 mmol/L.
3. Random venous plasma glucose taken at least two hours after eating or after taking 75 gm glucose is ≥11.1 mmol/L.
4. Presence of diabetic retinopathy.
5. Random sample on more than one occasion >11.1 mmol/L.

Diagnostic Criteria for Impaired Glucose Tolerance (IGT) and IFG (Impaired Fasting Glucose)

IGT: Venous plasma glucose concentration:
Fasting <6.1 mmol/L. 2 hours after 75 gm of glucose between 7.0 mmol/L and <11.1 mmol/L.

IFG: When fasting plasma glucose are >6.1, but <7.0.

Diagnostic criteria for GDM (pregnant female):

1. Fasting <7.0 mmol/L; 2 hr. after 75 gm glucose above >7.8 mmol/L.
2. Fasting >6.0, <6.9 mmol/L should be also considered to intervene in GDM.

Note:
PPG value may be 10% less in case of venous whole blood or 10% more in case of capillary blood.

Registration of a newly diagnosed case (first visit)

A. History

- Full Clinical History: Present illness, past illness, including history of malnutrition, drug history etc.
- Family History
- Scoio-Economic History
- Physical Examination: Height, Weight, BMI, BP, Cardiovascular, Respiratory, Alimentary, Endocrine, Neurological, Musculoskeletal system, including examination of peripheral pulse, and for evidence of malnutrition past or present.
- Ophthalmoscopic examination: Visual acuity, fundoscopy (dilated fundi) and fundus photography with fluoroscin angiography.

B. Investigation (initially at First Visit)

Blood

Two sample GTT in all suspected cases
Random one sample in already diagnosed case
HbA_1c – if not done within 2 months
Lipid profile, Urea, S. Creatinine, Blood count, SGPT
Urine
Glucose, protein and if indicated ketone bodies and microscopic examination test. Microalbuminuria if available in protein-negative cases.

Plain X-Ray of the abdomen and USG in patients below the age of 30 to exclude pancreatic calcification (If indicated).

C. Dietary Advice

Caloric intake must be individualized.

$$\frac{\text{Wt in Kg}}{}$$

Determine Body Mass Index (Ht in M^2) and ideal body weight.

Give emphasis on appropriate balanced diet specific to individual patient.

Aim

- Achieve and maintain desirable body weight
- Provide optimal nutrition
- Achieve normal/normal blood glucose, blood pressure and lipids level
- Avoid refined sugar, molasses, gur.
- Encourage high fiber diet-vegetable, legumes, whole gram, fruits etc.
- Minimum use of saturated, e.g. animal fat, dairy products, butter, ghee, coconut products. Hydrogenated vegetable oil etc.
- Food intake must be distributed evenly throughout the day except during the days of fasting (Ramadan). During Ramadan – follow the Ramadan diet.
- Artificial sweeteners containing sorbitol, saccharine or fructose is discouraged, non-caloric sweetener – e.g. aspartame may be used.
- Reduce salt intake. Always keep in mind about tendency of electrolyte imbalance in DM.

D. Educational advice:

I. Objective:

To promote compliance
To alleviate fear
To understand the disease and its complications with special emphasis on hypoglycaemia.
To understand its management – dose schedule of OHA, insulin, insulin technique.
To prevent omission of conventional management.

II. Plain

* To learn about management of sick days
* To alleviate fear – by telling that though uncontrolled diabetes may lead to many complication and early death, with proper control normal/near normal life and longevity can be achieved.
* To discuss about the symptoms, signs, complications and management of the disease, hypoglycaemia.
* To explain the cause and natural history of the disease.
* To outline the basic principle of management and target of control.
* To learn about foot care.
* For female of reproductive age learn about pregnancy planning and pre-conception planning.
* Available methods of contraceptives.
* To keep confidence about medical treatment and refrain from discontinuation of medication, delaying other modalities of treatment (traditional changes).

E. Exercise – Role of exercise in management of DM

It benefits:

Assists control of blood glucose, blood pressure and lipids
Helps to reduce and maintain ideal body weight
Prevents atherosclerosis, CHD, CVD, and PVD.
Improves insulin sensitivity, increase demand of blood supply of different vital tissues.

Precautions and Limitations:

Exercise has to be individualized. Start gradually with personal cardiac tolerance. Must not be excessive so to cause pain or inflict injury.

Contraindication: Coronary heart disease, proliferative retinopathy, severe neuropathy, neprhopathy, osteoarthritis, ketonuria.

Methods of exercise:

Stretching Exercise – Free hand exercise – 10 minutes to be followed by Aerobic Exercise – Duration at least 30 minutes i.e., brisk walking, swimming, cycling, jogging. Treadmill, static cycling etc at least 3 times a week.

Assessment of adequate exercise where no cardiac problem exist. Elevation of heart rate 200% times of basal rate.

F. Counseling regarding self care

a. Urine examination for glucose: Benedict's solution/examination by strips. Examine the urine four times daily, fasting, 2hABF, 2hAL, 2hAD. Record it in a notebook. Always second voided urine is to be tested.

Note: In some cases urine many be free from sugar, but blood sugar may be high. Urine examination therefore, has limited value, because of this high or low renal threshold.

b. Home Monitoring of Blood Glucose (HMBG):
Measurement of blood glucose is essential and ideal for the management of diabetes for the following reasons:

* To monitor daily control
* To detect hypoglycaemia and hyperglycaemic episodes
* To help proper management for sick days
* The frequency of HBGM should be adapted according to:
    1. Gycaemic status to adjust the OHA and/or insulin regimen,
    2. Age of the patient and
    3. Stability of the diabetes.

Information obtained from HMBG should be used in association with HBA_1c and clinical parameters to evaluate and modify management to improve glycaemic control. Initially FBS, 2hABF, 2hAL, 2hAD and late night are preferable.

HBA_1c (reflects glycaemic levels over the preceding 2 – 3 months) should be measured every 3 months (Four/yr). In case of children less than 6 years with unstable diabetes six HBA_1c measurement/yr is essential.

Fructosamine on the other hand, reflects the average glycaemic control of the previous 2 weeks. Thus fructosamine can be useful for practical purpose, especially for monitoring during pregnancy.

Treatment scheme: See Annex A,B & C.

At second visit (3 – 6 weeks)
Patients report to the doctor with reports of blood glucose level, fasting/random and also with the note book containing result of urine/blood glucose estimation at home. His weight is recorded. BP checked and diabetes control status reviewed.

Evaluation of dietary compliance, ascertain effectiveness of motivation and education.

Target for control

	Good	Fair	Poor
Fasting blood glucose (mmol/L)	4.4-6.1	<7.8	>7.8
Random blood glucose (mmol/L)	4.4-8.0	<10.0	>10.0
HbA_1c%	<7%	<8%	>8%
Total Cholesterol (mg/dl)	<200	≤250	>250
Triglycerides (mg/dl)	<150	≤180	>180
Body Mass Index	20-25	<27	>27
($kg/Meter^2$) Female	19-24	<26	>26
Blood Pressure (mmHg)	≤130/80	≤140/90	>140/90

Additional Targets:

Stop smoking and tobacco intake in any form. Avoid or limit alcohol.

Note:

1. In the elderly (55 years and above) the blood glucose may be relaxed adding 1.1 mmol/L for each decade.
2. In patients with retinopathy nad nephropathy the target BP should be <125/75 mmHg.

Third subsequent visit

1. For well – controlled patients requiring only diet and exercise once in every six months.
2. Fairly well-controlled every three months.
3. Poorly controlled patients need to be seen more frequently. Follow the same procedure as in second visit. If possible HbA_1c is to be estimated.
4. Consultant referral: Failure to control diabetes in 3 months time and if any complication related to diabetes is present.

Annual visit

All patients should have a detailed review once a year. This should include physical examination as on first visit, with inspection of the foot, peripheral pulses, teeth etc. Fundoscopy should be done in dilated fundi. Urine is tested for protein. HbA_1c, Cholesterol, (Chest X-Ray, ECG, if indicated)

Proteinuria, if absent, then microalbuminuria. Blood should also be tested for cholesterol and triglyceride, HDL, LDL level and S. Creatinine, Chest X-Ray and ECG, if indicated. If proteinuria is present 24 hour UTP, urine R/M/E, USG of KUB and other relevant tests

to evaluate the causes of proteinuria. Tests are done subsequently 3-6 months interval according to nature and severity of the renal problem.

TREATMENT SCHEME

Annexure `A'

Selection of modalities of treatment depends on:

(a) Type of Diabetes Mellitus
(b) BMI status
(c) Severity of hyperglycaemia
(d) Other associated complications.

Steps

1. Dietary modifications
2. Increased physical activities within patient's capabilities
3. If above two steps fail, pharmacological interventions.

Target of modalities of treatment are

1. To improve beta cell function
2. To reduce hepatic glucose output
3. To reduce insulin resistance in peripheral tissue i.e. muscles, adipose tissues.

Indication for Oral Hypoglycaemic Agents (OHA)

Patients without complications those whose blood glucose levels are elevated despite optimal diet and exercise therapy and in whom the following criteria have been excluded:

- History of ketosis/ketoacidosis (DKA/HONK)
- Pregnancy
- Acute stress, such as –
  * Infection
  * Trauma
  * Myocardial infarction

- Have blood glucose levels, which have been grossly elevated for the last three months HbA_1c >8.0%
- Have mild to moderate symptoms of hyperglycaemia
- Are preferably without the following diabetic complication.
  * Eye disease: Prolifertive retinopathy
  * Kidney disease: Serum Creatinine >2.5 mg/dl.
  * Acute metabolic neuropathy.

OHA

Three types of OHA

1. Secretagogues
2. Sensitizers
3. Reduced glucose absorption from GI Tract.

Guidelines

Mild Fasting Glucose (FPG) mmol/L <10.0 → Diet and Exercise
Moderate FPG >10.0 - <14.0 → Diet and Exercise.
Wait for 2 – 4 weeks, without improvement → Start OHA
Severe FPG >14.0 → Initiate insulin.

OHA therapy should be initiated with minimum effective dose. If necessary, may be increased gradually.

Insulin Secretagogues

A. Sulphonylurea

Examples	**Starting dose**	**Max. daily dose**
Glibenclamide (5 mg)	1.25 mg – 2.5 mg	15 mg
Glipizide (5 mg)	2.5 mg – 5 mg	40 mg
Gliclazide (80 mg)	20 mg – 40 mg	320 mg
Glimepride	0.5 mg	6 – 8 mg

Dose may be increased every 1 or 2 weeks, until desirable glycaemia is achieved or the maximum dose is reached. Blood glucose should be monitored by the patient: fasting or post-prandial, for at least two days each week.

Preferably single dose as the drugs have long plasma half life. If high dose is to be given the two divided dose may be tried but not in three divided doses.

B. Glinides

Examples	Starting dose	Max. daily dose
Rapaglinide	0.5 mg 3 times before meal	8 mg
Nateglinide	120 mg 3 times before meal	360 mg

The tablet should be taken 10 – 20 minutes before breakfast.

- Short acting medicine
- Suitable for post prandial surge
- Suitable for patients with irregular meal habits.

Duration of action : 2 – 4 hours, onset of action after 5 – 10 min.
D**rug schedule:** 1 – 3 according to blood profile.
No meal: no dose.
Preferable, where hypoglycaemia tendency is more. Old age particularly reluctant to take food in amount and frequency.

CAUTION

OHA should be avoided in conditions predisposed to renal impairment (S. Creatinine >2.5). [OHA is excreted by kidney. Particularly glibenclamide; gliclazide, glipizide should be used with caution]. Hepatic impairment acute and chronic diseases.

2. Insulin Sensitizers

A. Biguanides:

Example	Starting dose		Maximum dose
Metformin	500 mg 850 mg	500 mg 1-3 divided dose with meals	3000 mg 3 divided dose

Tablets to be taken with or just after meal.

B. Thiazolidinediones

- Rosiglitazone	4 mg 8 mg	4 mg once daily morning	8 mg
- Pioglitazone	15 mg 30 mg	15 mg once daily morning	45 mg

Contra-indications:

Hepatic and renal impairment (S. Creatinine > 2.5 mg/dl) increasing proteinuria, predisposition to lactic acidosis, heart failure, severe infection or trauma, dehydration, pregnancy and lactation.

3. Others

Acarbose 50 mg	25 – 50 mg 1 – 3 times with first bite of meal		300 mg in divided dose

Practical Points

Before initiating the OHA, LFT, RFT should be done as all OHA are metabolised by the liver and excreted either by kidney or liver. During course of treatment liver and renal function should be monitored wherever indicated and suspected.

Special Notes:

a. Pre-pregnancy planning: Any woman if wants pregnancy must plan it much before.

b. Stop OHA, start insulin, if required for very good control or near-normal figures before conception.
c. Insulin to be used throughout pregnancy.

Annexure 'B'

Insulin

Insulin therapy is indicated in those who meet the following criteria:

1. Type 1 DM patients
2. Type 2 DM patients who remain persistently symptomatic hyperglycaemic on maximum dose of oral agents and diet (primary/secondary failure).
    - Under stress (i.e. acute infections, myocardial infarction etc.)
    - Diabetes with advanced complication;
    - Symptomatic hyperglycaemia;
    - Lean, symptomatic patients;
    - Prior to surgery;
    - At least 3-4 months planning prior to conception;
    - Throughout pregnancy;
    - Also, if planning for pregnancy.

Following insulin regimen may be tried:

When initiating insulin therapy regimen of two injections per day is recommended (0.2 – 0.4 unit/kg body wt/day), depending on the level of FBG, two-third of the dose may be given in the morning BBF and one-third at night BD.

Two injection per-day with split-mixed or pre-mixed insulin therapy

Two injections per day with split or mixed regimen is preferred for type 2 DM patients. There is no definite rule of split regimen. However, Insulin therapy may be started with 0.2 to 0.4 units insulin/kg body weight/day divided in two-to-one morning and evening ratio. An example is shown below:

- 2:1 or 1:1 parts intermediate and one part rapid acting insulin one-half hour before breakfast, (total 2/3 of the dose).
- 2:1 or 1:1 ratio of each one half before the evening meal (total 1/3 of the dose).

For example: If a person weighing 60 kg needs 24 units/day, then 16 units would be given in the morning and 8 units would be given in the evening. The 16 units' morning dose should be divided into 8 units' intermediate and 8 units' acting. The evening dose should be 4 units each for a one to one ratio.

- It is best to start with a low dose and the patient's response to be assessed. If target is not achieved, the insulin dosage may be gradually increased every 3-7 days.

NB: There are various combinations of premixed insulin available (e.g. 30/70, 50/50). Dose and type of premixed preparation should be adjusted individually with frequent blood glucose monitoring.

Three Injections per day (Regular Insulin)

Three Injections per day regimen is used for type 2 DM and some type 1 DM patients as in surgery, pregnancy and other emergencies. Time of injections is usually before major meals (Breakfast, Lunch and Dinner). But on many occasions, this type of regimen fails to control fasting hyperglycaemia. In such situations evening dose should be mixed with intermediate acting insulin or separately intermediate insulin may be added at bed time.

Increasing the dose of insulin

Persistent presence of urine sugar continuing over 2-3 days, combined with elevated blood sugar levels, indicates poor control and increased insulin requirement. Here again, the first step is to ascertain whether any dietary error could account for the deterioration in control. Once the possibility has been excluded the dose of insulin should be increased by 2-4 units. If the above measures fail to achieve normoglycaemia then following measures may be taken.

Examples:

1. If breakfast and pre-lunch BG and/or urine glucose is high for a few days then add short acting insulin before breakfast. But the increment should not be more than 2-4 units a time.
2. Similarly, if post lunch and pre-dinner BG or urine is high, then increase morning dose of intermediate acting insulin by 2-4 units.
3. If post dinner and late light BG or urine sugar is high, and short acting insulin 2-4 units before dinner.
4. If fasting BG or urine sugar is high then increase pre-dinner intermediate acting insulin.

Reducing of Insulin Dose

Consistently low blood sugars, negative urine sugars and definite signs of hypoglycaemia indicate that the dose of insulin is too high. Steps may be followed to reduce the insulin dose according to BG.

Combination therapy in the treatment of Diabetes Mellitus

As Diabetes Mellitus is a long life metabolic disorder, compliance and acceptability of patient is the key point for good glycaemic control. Cost effectiveness, interference of daily lifestyle greatly influences patient compliance. Considering all these points, combination therapy has been introduced. A good number of therapeutic trials and studies were done to support this theme. Combination therapy can be given in the following different modalities keeping in mind about degree of contribution of β-cell dysfunction and insulin resistance.

1. Suphonylurea + Biguanides
2. Sulphonylurea + Insulin
3. Insulin + Biguanides
4. Insulin + Biguanides + Sulphonylurea
5. Non-sulphonylurea + Biguanide + Glitazone
6. Sulphonylurea + Acarbose
7. Metformin + Acarbose
8. Acarbose + Insulin
9. Repaglinide + Pioglitazone/Rosiglitazone (FDA approved).

A Guideline for combination therapy

Obese Type 2 DM Start first with biguanides – if fails with maximum dose add Sulphonylur or any insulin secretagogue or glitazone or acarbose or minimum amount of insulin.

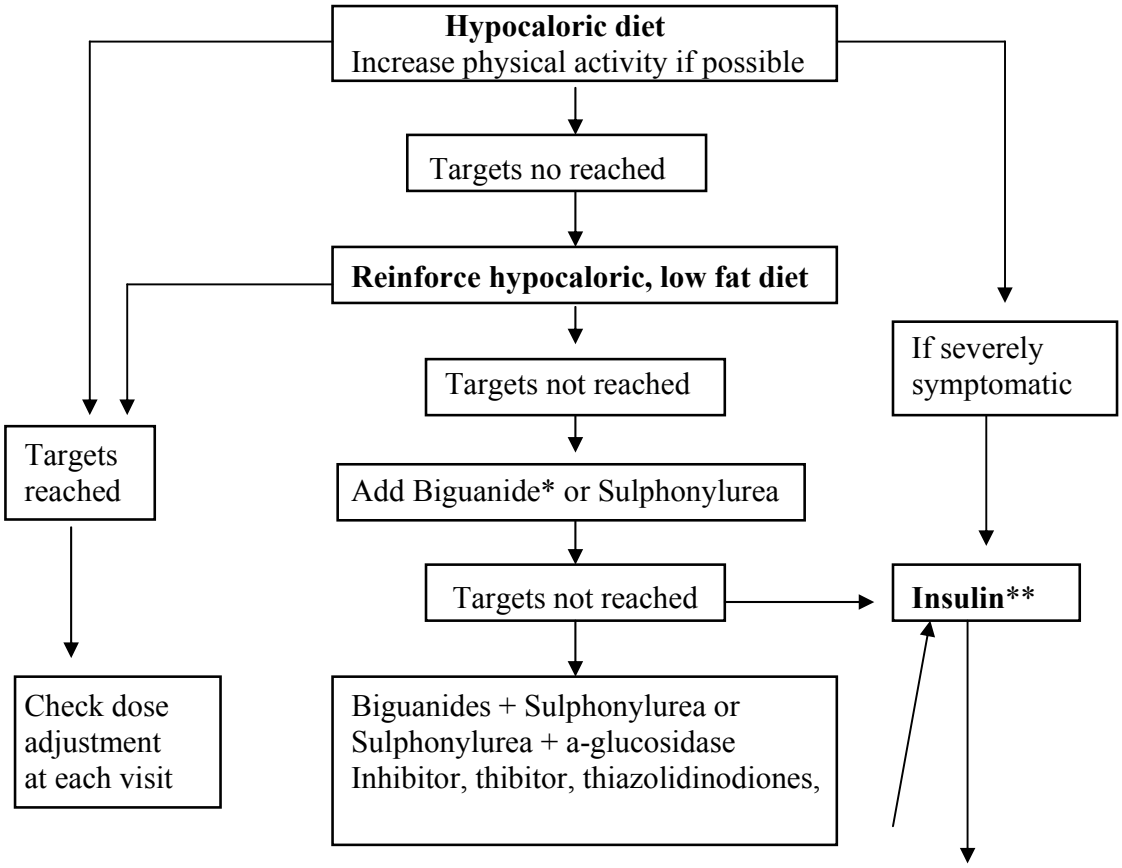
Normal weight Type 2 DM Start with sulphonylurea if fails with moderate dose of OHA or you may add biguanide/glitazone add insulin in moderate dose.

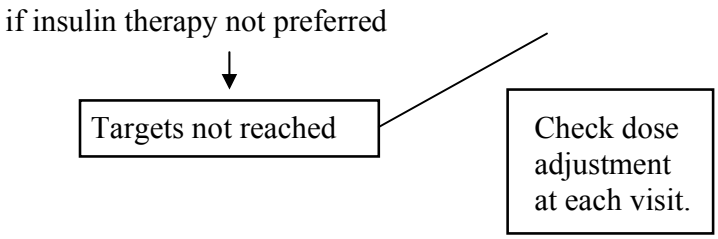
Under-weight Type 2 DM Start with insulin then add minimum sulphonylurea

Under-weight Type 2 DM Never use biguanides. When there is tendency of over-weight, then add biguanide.

Treatment scheme

1. Obese diabetic



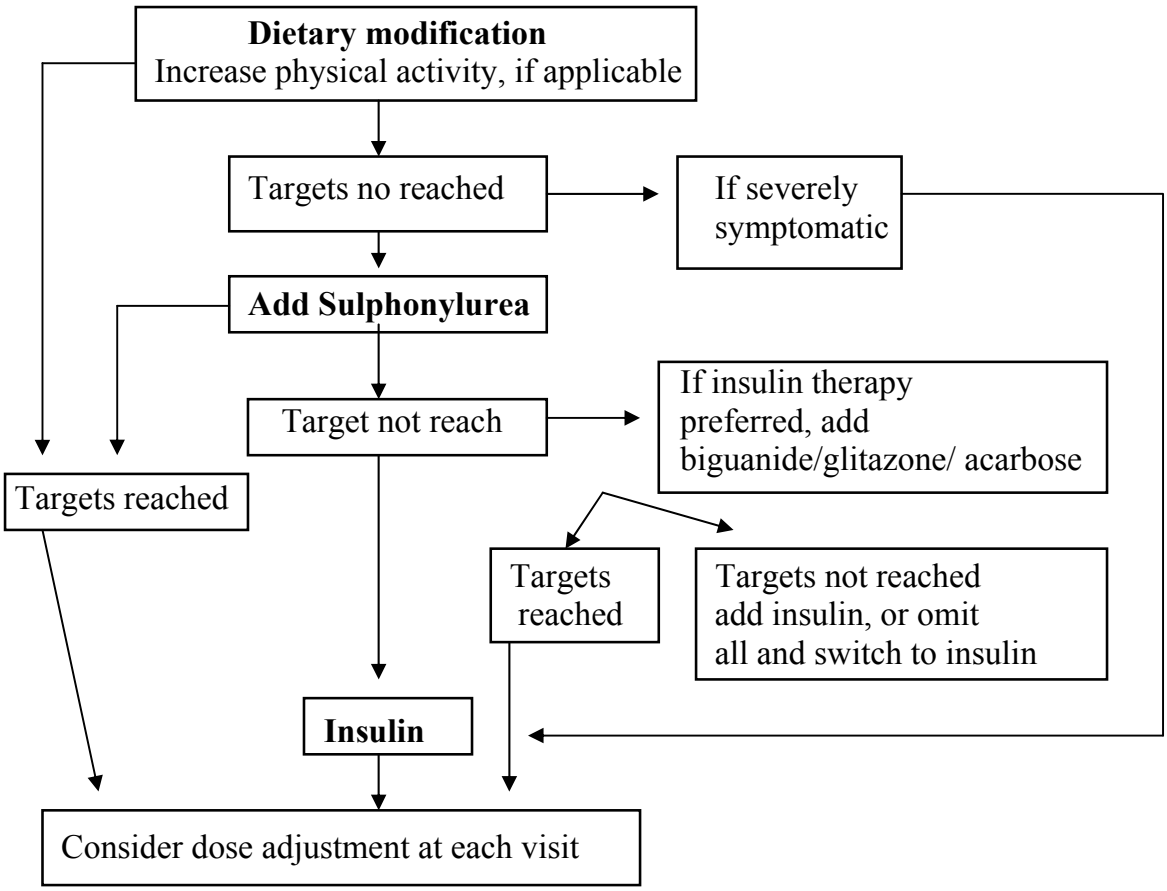


* Unless contraindications present
** May be combined with oral agent

NB: Define individual

Treatment scheme

1. Non-obese diabetic



N.B: Define individual aims of therapy

SCREENING OF ASYMPTOMATIC NON PREGNANT INDIVIDUALS

All patients over the age of 40 years should be screened. As far as possible venous plasma glucose should be used. Urine glucose is regarded as the second alternative.

1. Blood Glucose
   Random sample 7.8 mmol/L as cut off point. If reflectane – meters are used for screening it must be done by trained person (as quality assurance).

2. Spot Urine
   Random sample (preferably 1 hour post meal) (Use Glucose Oxidase Dipstick only)

Frequency: Yearly in high risk group. Every two years for others.

High Risk Group:

- Age above 40 years
- Obesity
- Positive Family History (Especially those with Hypertension and Hyperlipidaemia)
- Females with previous Gestational Diabetes.

DIAGNOSIS

Only blood glucose should be used for diagnosis.

WHO Criteria* for diagnosis
Venous Plasma

FBS	$\geq$ 7.0 mmol/L
2 hours AG	>11.1 mmol/L

If other samples are used e.g. venous whole blood.

Use Glucose oxidase or Hexokinase method in a reference laboratory.
Use of reflectance meters is not acceptable for diagnosis at present.

1. For those asymptomatic subjects with positive urine and blood screening, perform formal random blood glucose test (2 hours post prandial) on separate occasions.
2. For diagnosis of Diabetes Mellitus in asymptomatic subjects Random Blood Sugar (RBS) must be >11.1 mmol/L on two separate occasions.

New Diagnostic Criteria proposed by American Diabetes Association

Criteria for the diagnosis of diabetes mellitus

1. Symptoms of diabetes plus casual plasma glucose concentration 20 mg/dl (11.1 mmol/L). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes includes polyuria, polydipsia, and unexplained weight loss.

or

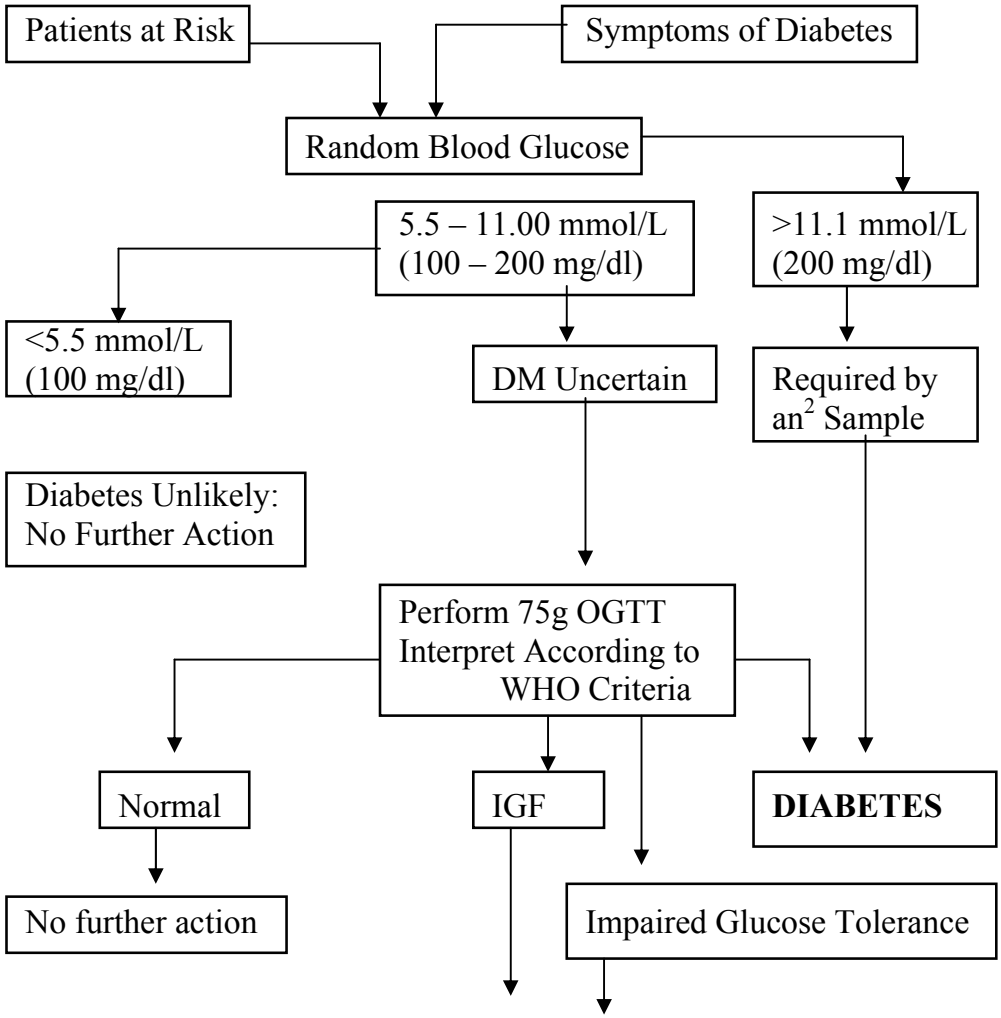
2. FPG >126 mg/dl (7.0 mmol/L). Fasting is defined as no caloric intake at least 8 h.

or

3. 2- PG >200 mg/dl (11.1 mmol/L) during an OGTT. The test should be performed as described by WHO (1985), using glucose load containing the equivalent of 75g anhydrous glucose dissolved in water.

In the absence of unequivocal hyperglycemia with acute metabolic decompensation, these criteria should be confirmed by repeat testing on a different day. The third measure (OGTT) is not recommend.

Screening and diagnosis algorithm
Based on Venous Plasma Glucose



Follow – up

Diagnosis values for the OGTT
Glucose concentration, mmol/litre (mg/dl)

	Whole blood		Plasma	
	Venous	Capillary	Venous	Capillary
DM – Fasting value	≥6.7 (≥120)	≥6.7 (≥120)	≥7.0 (≥140)	v7.8 (≥140)
2 HG	≥10 (≥200)	≥11.1 (≥200)	≥11.1 (≥200)	≥12.1 (≥200)
IGT – Fasting value	<6.7 (<120)	<6.7 (<120)	<7.0 (<140)	<7.8 (<140)
2 HG	6.710.0 (120-180)	7.811.1 (140-200)	7.8-11.1 (140-200)	8.9-12.2 (160-220)