CLINICAL PRACTICE GUIDELINES

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MANAGEMENT OF TYPE 2 DIABETES MELLITUS

Third Edition
(2004)

MINISTRY OF HEALTH MALAYSIA

PERSATUAN DIABETES MALAYSIA (PDM)

ACADEMY OF MEDICINE

Statement of Intent

This guideline is meant to be a guide for clinical practice, based on the best available evidence at the time of development. Adherence to this guideline may not necessarily guarantee the best outcome in every case. Every health care provider is responsible for the management of his/her unique patient based on the clinical picture presented by the patient and the management options available locally.

Review of the Guidelines

This guideline was issued in Sept. 2004 and will be reviewed in Sept. 2007 or sooner if new evidence becomes available

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PREFACE

A tremendous body of evidence has become available in the last 6 – 8 years that has made a major impact on diabetes management. From new targets for control, emphasis and recognition of the cluster of cardiovascular risk factors that make up the metabolic syndrome in which type 2 diabetes is a principal player and new pharmacologic agents, these have changed the algorithms for diabetes care.

This new edition of the CPG for type 2 diabetes mellitus will address many of these changes. Particular emphasis has been made on the new glycaemic targets for control. The HbA_{1c} target for good glycaemic control has been reduced to 6.5% following the results from the UKPDS that showed that there is no level below which there is continued reduction in risk for complications. Availability of newer pharmacologic agents that work on different pathophysiologic mechanisms as well as the advent of newer insulins that have a better safety profile make it possible to achieve these lower glycaemic targets with lower risk of hypoglycaemia. In addition, recognition of the cluster that makes up the metabolic syndrome emphasizes the need to aggressively control blood pressure, lipids and overweight/obesity in order to maximally reduce the rate of macrovascular complications.

The key component of diabetes care remains the provision of diabetes education in order to achieve best results in intensive self-management. Diabetes Care is not the domain of any particular group of the health professionals. It requires an integrated and holistic approach to chronic disease management in order to increase patient motivation, compliance and ultimately result in achievement of good glycaemic control.

Early intervention during the course of the disease will decrease the risk of complications thereby reducing healthcare cost. It has been clearly demonstrated that economic losses can be greatly reduced by investing in promotive and preventive programmes particularly with regards to early detection of disease and prevention of complications. The system of care and monitoring provided in the previous CPG remains intact but adds new evidence for targets for control.

The prevalence of type 2 diabetes continues to rise inexorably with much of the global burden expected to come from the Western-Pacific as well as the South East Asian region.

It continues to be vital that Diabetes Care be co-ordinated properly and systematically at all levels of health care. This clinical practice guideline on the management of type 2 diabetes is an updated version of the second document of 1996. This updated edition provides a comprehensive approach focusing on treatment strategies.

As chairperson, I wish to thank everyone involved in developing this guideline and particularly members of the task force team for their valuable contributions to these revised, expanded and comprehensive guideline.

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GUIDELINE OBJECTIVES

Objectives

The aim of the guideline is to provide evidence based recommendations to assist health care providers in the identification, diagnosis and management of people with type 2 Diabetes Mellitus. It also includes a section on pre-diabetes and prevention of progression in the high-risk population and Metabolic Syndrome.

Clinical Questions

The clinical questions of these guidelines are:

1. How can diabetes be prevented.
2. How is screening for diabetes be carried out.
3. How is diabetes diagnosed.
4. How can people with diabetes be managed?

Target Population

This guideline is applicable to people with diabetes as well as those at risk of developing diabetes.

Target Group

This guideline is meant for all general practitioners and those providing primary care for people with diabetes as diabetes is a common disease.

Evidence, Identification and Search Strategy

The evidence presented in this guideline was collated from the following sources:

1. Systematic review of relevant published literature (up to 2004) as identified by electronic (e.g. Medline) search.
2. American Diabetes Association. Position Statement on Standards of Medical Care for Patients with Diabetes Mellitus, 2003.
3. International Diabetes Federation. Guidelines for Type 2 Diabetes Mellitus, 1999.
4. Malaysian CPG on Management of Obesity (In Press)
5. United Kingdom Prospective on Diabetes Study.
6. Clinical Guidelines and Evidence Review for Type 2 Diabetes Management of Blood Glucose, Sheffield: ScHARR, university of Sheffield 2001.
7. Canadian Clinical Practice Guidelines 2003.

Key to Evidence Statements and Grades of Recommendations

The definition of types of evidence and the grading of recommendation used in this guideline originate from the Canadian Preventive services Task Force and are set out in the following tables:

LEVELS OF EVIDENCE

I	Evidence obtained from at least one properly randomized controlled trial
II – 1	Evidence obtained from well-designed controlled trials without randomization
II – 2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group
II – 3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence
III	Opinions of respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees

SOURCE: U.S. / CANADIAN PREVENTIVE SERVICES TASK FORCE

GRADES OF RECOMMENDATIONS

A	At least one meta analysis, systematic review, or RCT, or evidence rated as good and directly applicable to the target population
B	Evidence from well conducted clinical trials, directly applicable to the target population, and demonstrating overall consistency of results; or evidence extrapolated from meta analysis, systematic review, or RCT
C	Evidence from expert committee reports, or opinions and /or clinical experiences of respected authorities; indicates absence of directly applicable clinical studies of good quality

SECTION 1 SCREENING AND DIAGNOSIS

1.1 OBJECTIVE

To assess specific high risk population groups for detection of diabetes and ensure timely and appropriate management.

1.2 STRATEGY

- Opportunistic Screening.
- Selective according to screening criteria.

1.3 TARGET POPULATION

This guideline is applicable to high-risk individuals who present themselves to a health or medical facility.

1.4 TRAGET GROUP

This guideline is meant for all any healthcare professionals who manage diabetes.

1.5 WHO SHOULD BE SCREENED

a) Any person found to have symptoms of diabetes mellitus (tiredness, lethargy, polyuria, polydipsia, polyphagia, weight loss, pruritus vulvae, balanitis) must be screened.
(American Diabetes Association, ADA 2004)

b) Any person who presents to a primary care facility for any reason, without symptoms of diabetes, but has any ONE of the following risk factors should be screened:

- Age 35 years or older
- Pre-obese, BMI > 23 kg/m^2
- History of Gestational Diabetes Mellitus
- History of big baby (birth weight ≥ 4.0kg)
- History of diabetes mellitus in first degree relatives (parents, siblings)
- Hypertension (140/90 mmHg)
- Hyperlipidaemia
- Dyslipidaemia either HDL-cholesterol < 0.9 or Triglyceride > 1.7 mmol/L

c) Pregnant women should be screened at least once at ≥ 24 weeks of gestation. Screening at an earlier stage of gestation depends on degree of suspicion and at the physician's / obstetrician's request.

1.6 SCHEDULE

Table 1: Schedule of the Screening Programme

Criteria	*Frequency*
With one or more of the above risk factors	Annually
Age 35 to 40 years without any risk factors	Every 2 years
Age ≥ 40 years	Annually

1.7 SCREENING TEST

- Screening can be done by measuring random blood glucose (capillary blood), using glucose meters and strips.
- Screening process as in Flow Chart 1 (Appendix 1a) and Flow Chart 2 (Appendix 1b)

1.8 DIAGNOSIS

- Diagnosis must be confirmed by measurement of venous plasma glucose.
- Venous sample for plasma glucose should be taken prior to initiating therapy[15].

Table 2 : Values for Diagnosis

	Fasting	**Random**
Plasma Venous Glucose	≥ 7.0 mmol/L	≥ 11.1 mmol/L

- In the symptomatic patient, one abnormal glucose value is diagnostic
- In the asymptomatic patient, 2 abnormal glucose values are required
- OGTT is recommended in the following:
  - Patients at high risk of developing diabetes mellitus but do not have plasma glucose values in the diabetic range
  - Patients at high risk of developing diabetes mellitus with borderline plasma glucose values of 5.6-6.9mmol/L (fasting) or 6.5-11.0mmol/L (random)

Table 3 : Diagnostic values for Type 2 Diabetes/Glucose Intolerance – OGTT (ADA 2004[114])

OGTT Plasma Glucose Values (mmol/L)		
Category	**0-hour**	**2-hour**
Normal	≤ 5.6	< 7.8
IFG	5.6 – 6.9	-
IGT	-	7.8 – 11.0
DM	≥ 7.0	≥ 11.1

Recommendation : Screening and Diagnosis

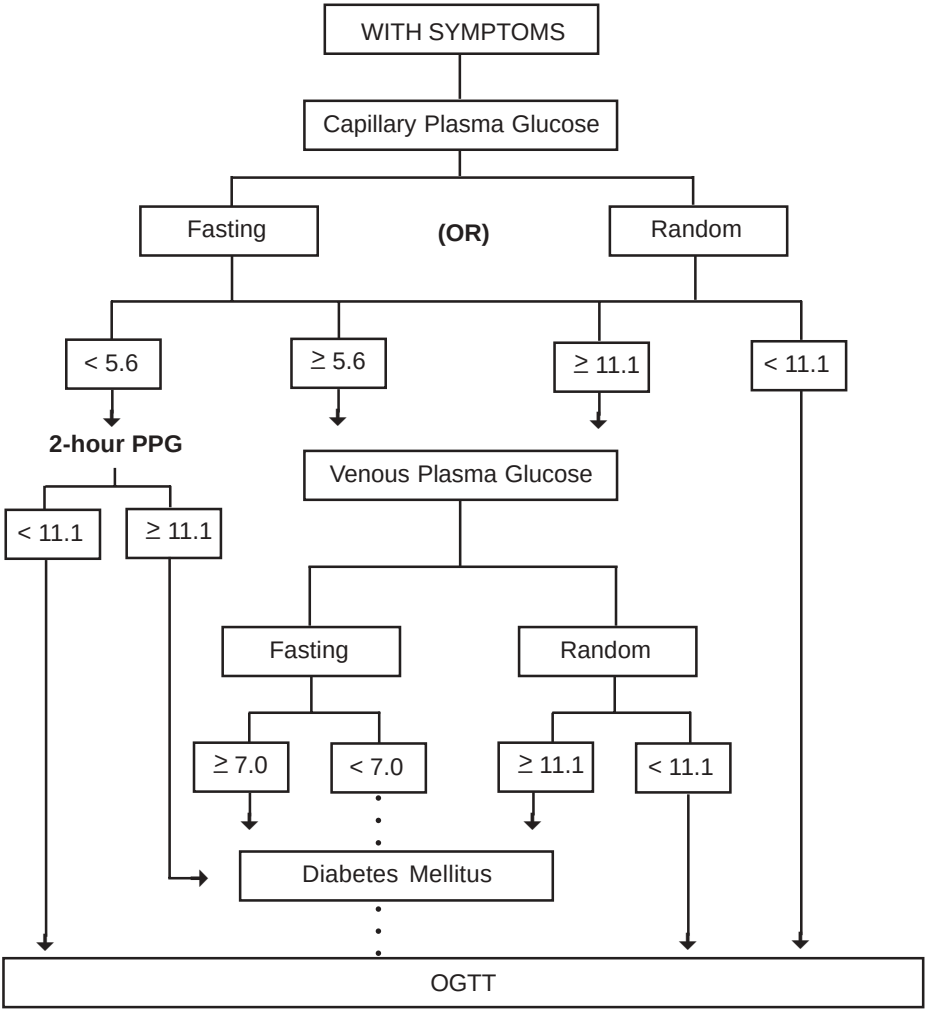
1. Screening for diabetes using FPG should be performed every 2 years in individuals 35 - 40 years of age without risk factors and those who have one or more risk factors or age ≥ 40 should have annual screening. *[Grade C, Consensus]*

2. More frequent and/or earlier testing with either an FPG or 2hPG in a 75-g OGTT should be considered in people with additional risk factors for diabetes. *[Grade C, Consensus]*

3. Testing with a 75-g OGTT should be considered in individuals with an FPG of ≥ 5.6 to 6.9 mmol/L in order to identify individuals with IGT or diabetes. *[Grade C, Consensus]*

SCREENING PROCESS:

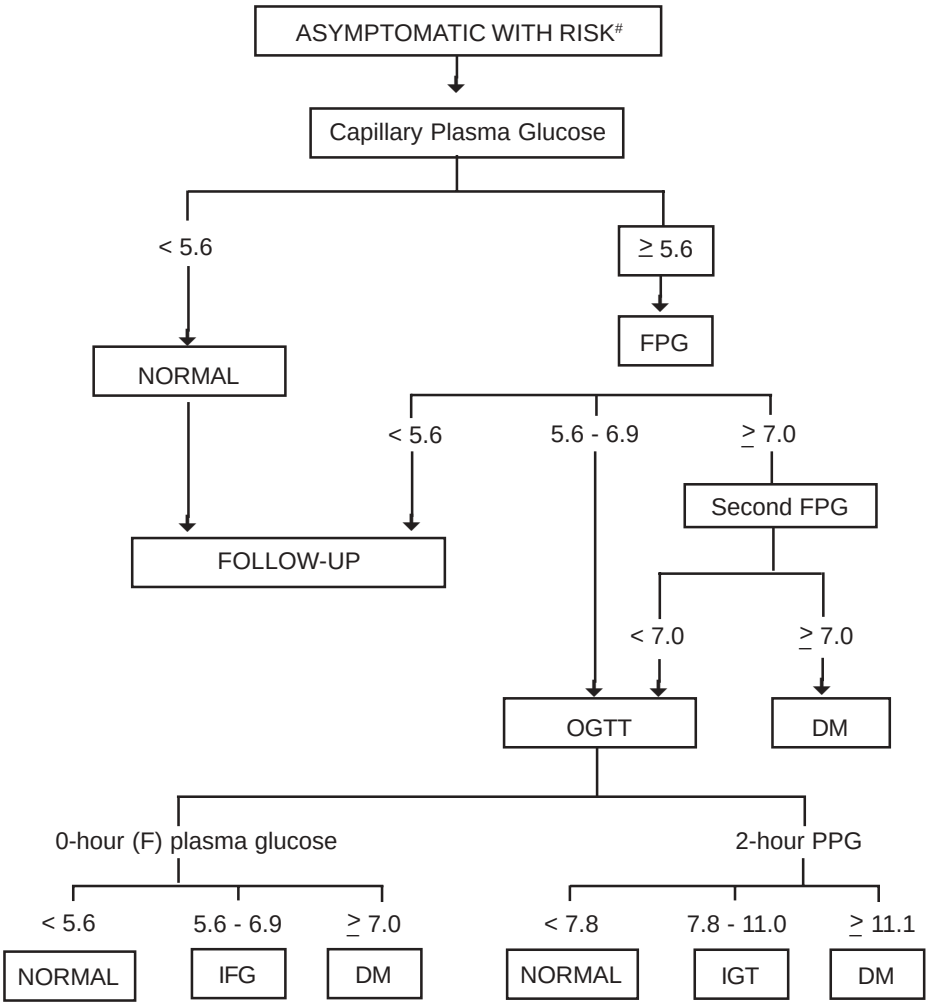
Algorithm 1: Screening for type 2 Diabetes Mellitus at Primary Care Level - with symptoms†



**All values are in mmol/l. For glucometers reading whole blood glucose values decrease by 12%*

†Values / cut-off points are as recommended by IDF[5]

Algorithm 2: Screening for type 2 Diabetes Mellitus at Primary Care Level – without symptoms[†]



[*]All values are in mmol/l. For glucometers reading whole blood glucose values decrease by 12%

[†]Values / cut-off points are as recommended by IDF[5]

SECTION 2 MANAGEMENT FOR TYPE 2 DIABETES

Diabetes management involves patient education, exercise and medication.

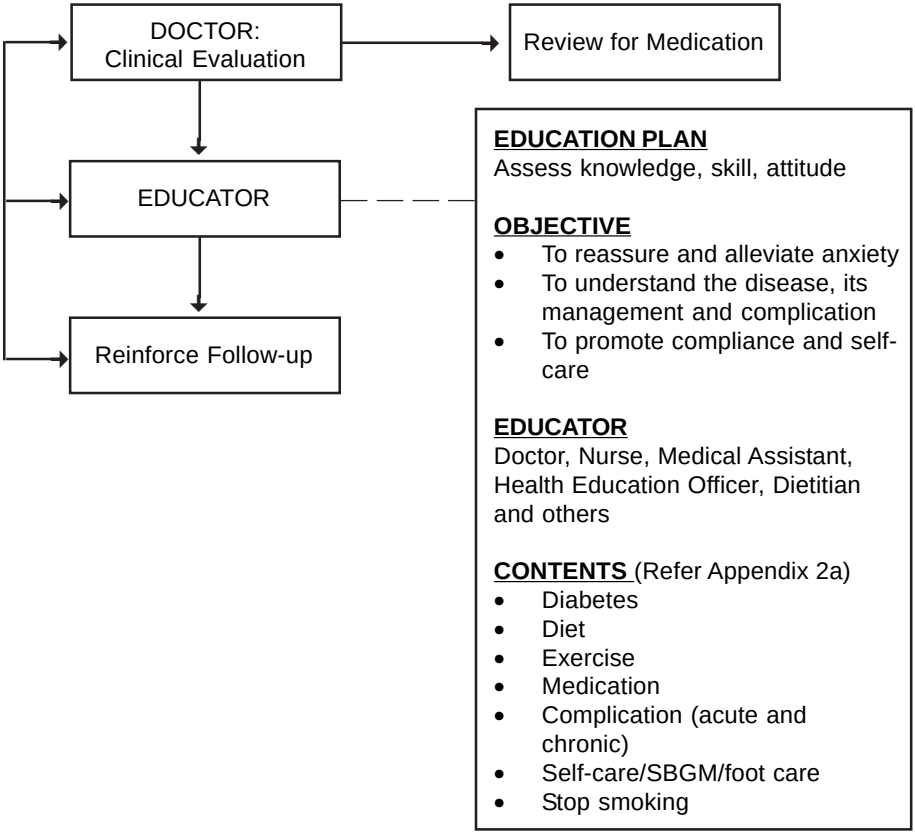
Targets for Control [2] [3]

Table 4 : Targets for Type 2 Diabetes Mellitus

	Levels
Glycaemic Control	
Fasting	4.4 – 6.1 mmol/l
Non-fasting	4.4 – 8.0 mmol/l
HbA_{1c}	< 6.5 %
Lipids	
Triglycerides	≤ 1.7 mmol/l
HDL-cholesterol	≥ 1.1 mmol/l
LDL-cholesterol	≤ 2.6 mmol/l
Body mass index[4] (BMI)	< 23 kg/m^2
Blood Pressure	
Normal Renal Function [5] [6]	≤ 130/80 mmHg
Renal Impairment /Gross Proteinuria	≤ 120/75 mmHg

A DIABETES EDUCATION

Algorithm 3: Education Strategies



Health education, diet therapy and exercise must be reinforced.

B LIFESTYLE MODIFICATION

B1 DIET THERAPY

Dietary management is one of the cornerstones in diabetes management. Effective management of diabetes cannot be achieved without a proper diet even when medication has been initiated.

The following are general recommendations:

1. Nutrition counseling by a dietitian is recommended. *[Grade C, Consensus]*

2. To meet their nutritional needs, dietary recommendations should be individualized. *[Grade C, Consensus]*

3. Sucrose and sucrose-containing foods can be substituted for other carbohydrates as part of mixed meals up to a maximum of 10% of energy, provided adequate control of glucose and lipids is maintained. *[Grade* B[7], [8]*]*

4. All people with diabetes should restrict intake of saturated fats and trans fatty acids to <10% of energy. Meal plans should favour monounsaturated fats, when possible, and include foods rich in polyunsaturated. *[Grade C, Consensus]*

5. A weight-loss goal of 5 to 10% of body weight over an initial 6-month period should be recommended to improve overall metabolic and glycaemic control in obese people with type 2 diabetes. *[Grade C, Consensus]*

B2 PHYSICAL ACTIVITY

Types of physical activity:

- Any increase in physical activity is beneficial, e.g. walking, gardening, cycling. (Refer Appendix 2b)

Implementing exercise programme:

- Regular physical activity is recommended. The type and intensity should be individualized.
- Preferably daily minimum 3 – 5 times per week, at least 30 minutes/session
- The benefits of physical activities is cumulative (e.g. three 10 minute sessions in a day is equivalent to a 30 minute session)
- A stress ECG stress test should be considered for previously sedentary individuals with diabetes at high risk for CVD who wish to increase their physical activity. *[Grade C, Consensus]*

C. MEDICATION

C1.1 Oral Agent Monotherapy

If glycaemic control is not achieved (HbA_{1c} > 6.5% and/or; FPG > 7.0 mmol/L or; RPG >11.0mmol/L) with lifestyle modification within 1 –3 months, ORAL ANTI-DIABETIC AGENT should be initiated [9](UKPDS, 1998).

In the presence of marked hyperglycaemia in newly diagnosed symptomatic type 2 diabetes (HbA1c > 8%, FPG > 11.1 mmol/L, or RPG > 14 mmol/L), oral anti-diabetic agents can be considered at the outset together with lifestyle modification. *[Grade C, Consensus]*

As first line therapy:

- Obese type 2 patients, consider use of metformin [10]*[UKPDS, 1998]*, acarbose[+] or TZD[#]
- Non-obese type 2 patients, consider the use of metformin or insulin secretagogues

Metformin is the drug of choice in overweight/obese patients. TZDs and acarbose are acceptable alternatives in those who are intolerant to metformin [11, 12].
If monotherapy fails, a combination of TZDs, acarbose and metformin is recommended [13,14,15,16,17]. If targets are still not achieved, insulin secretagogues may be added [18](SDM, 2000).

C1.2 Combination Oral Agents

Combination oral agents is indicated in:

- Newly diagnosed symptomatic patients with HbA_{1c} >10
- Patients who are not reaching targets after 3 months on monotherapy

[Grade C, Consensus]

C1.3 Combination Oral Agents and Insulin

If targets have not been reached after optimal dose of combination therapy for 3 months, consider adding intermediate-acting/long-acting insulin (BIDS). Combination of insulin + oral anti-diabetic agents (BIDS) has been shown to improve glycaemic control in those not achieving target despite maximal combination oral anti-diabetic agents.[19] *[Grade A]*

Combining insulin and the following oral anti-diabetic agents has been shown to be effective in people with type 2 diabetes:

- Biguanide (metformin)[20] [21] [22] *[Grade A]*
- Insulin secretagogues (sulphonylureas)[23] *[Grade A]*
- Insulin sensitizers (TZDs)[24] *[Grade A]* (the combination of a TZD plus insulin is not an approved indication)
- α-glucosidase inhibitor (acarbose)[25] [26] *[Grade A]*

Insulin dose can be increased until target FPG is achieved. If glycaemic targets are not achieved, monitor postprandial glucose.

(Refer to Appendix 2c)

C1.4 Insulin Therapy

Short-term use:

- Acute illness, surgery, stress and emergencies (refer Appendix 2g)
- Pregnancy (refer Appendix 2f)
- Breast-feeding
- Insulin may be used as initial therapy in type 2 diabetes [1] *[Grade A]* particularly in marked hyperglycaemia *[Grade C, Consensus]*
- Severe metabolic decompensation (diabetic ketoacidosis, hyperosmolar non-ketotic coma, lactic acidosis, severe hypertriglyceridaemia)

Long-term use:

- If targets have not been reached after optimal dose of combination therapy or BIDS, consider change to multi-dose insulin therapy. When initiating this, insulin secretagogues should be stopped and insulin sensitisers e.g. metformin or TZDs, can be continued (refer Appendix 2c).

C2.1 General Guidelines for Use of Oral Anti-Diabetic Agent (ODA) in Diabetes

- In elderly non-obese patients, short acting insulin secretagogues can be started but long acting Sulphonylureas are to be avoided. Renal function should be monitored
- Oral anti-diabetic agent s are not recommended for diabetes in pregnancy
- Oral anti-diabetic agents are usually not the first line therapy in diabetes diagnosed during stress, such as infections. Insulin therapy is recommended for both the above
- Targets for control are applicable for all age groups. However, in patients with co-morbidities, targets are individualized
- When indicated, start with a minimal dose of oral anti-diabetic agent, while re-emphasizing diet and physical activity. An appropriate duration of time (2-16 weeks depending on agents used) between increments should be given to allow achievement of steady state blood glucose control

C2.2 Oral Anti-Diabetic Agents

There are currently four classes of oral anti-diabetic agents:

i. Biguanides
ii. Insulin Secretagogues – Sulphonylureas
iii. Insulin Secretagogues – Non-sulphonylureas
iv. α-glucosidase inhibitors
v. Thiazolidinediones (TZDs)

i. Biguanides

- Biguanides do not stimulate insulin secretion, and lowers glucose by decreasing hepatic glucose production. It can lower plasma glucose by up to 20% as first line drug treatment especially in the overweight/obese patient
- Metformin in combination with other oral anti-diabetic agents have synergistic effect to further reduce blood glucose. Metformin can increase insulin sensitivity and reduce insulin requirements

Dosage: Metformin 500 mg tablet

Initial dose	500 mg daily increasing to 500 mg twice daily after 1 week, to minimise gastrointestinal side effects. The side effects can be further reduced by taking it with food
Usual dose	500 mg TDS
Maximum dose	1.0g BD

Metformin retard 850 mg tablet (slow release formulation)

Usual dose	BD
Maximum dose	1700 mg OM / 850 mg ON

Caution:

- Should not be used in patients with impaired renal function (serum creatinine > 130 µmol/l or creatinine clearance < 60 mL/min[1]), liver cirrhosis, congestive cardiac failure, recent myocardial infarction, chronic respiratory disease, vascular disease and severe infections or any conditions that can cause lactic acid accumulation
- Vitamin B12 deficiency may occur if metformin is given to patients who have had partial gastrectomy and terminal ileal disease

ii. Insulin Secretagogues

a) Sulphonylureas

- Sulphonylureas lower plasma glucose by increasing insulin secretion. They can lower plasma glucose by up to 25%
- Sulphonylureas should be taken 30 minutes before meals, except glimepiride and gliclazide MR which can be taken just before the meal
- Second generation Sus (glimepiride and gliclazide MR) cause less risk of hypoglycaemia and less weight gain
- Sulphonylureas can be combined with other Oral Anti-Diabetic Agents or insulin to improve glucose control, if indicated

- Compliance may be improved with daily dosing Oral Anti-Diabetic Agent
- Combining 2 different Sulphonylureas / insulin secretagogues is not recommended
- Side effects of Sulphonylureas are rare and include hepatitis, SIADH, blood dyscrasias

Dosage

Drug	Minimum Dose	Maximum Dose	Duration
Chlorpropamide (Diabenese)	125 mg OM	500 mg OM	Very long
Glibenclamide (Daonil, Euglucon)	2.5 mg OM	10 mg BD	Long
Gliclazide (Diamicron)	40 mg OM	160 mg BD	Medium
(Diamicron MR)	30 mg OM	120 mg OM	Long
Glipizide (Minidiab)	2.5 mg OM	10 mg BD	Medium
Glimepiride (Amaryl)	1 mg OM	6 mg OM	Long

Note:

- Chlorpropamide is no longer recommended because of its extremely long half-life
- Glibenclamide is metabolised by the liver but its metabolites are active and excreted by the kidney. The drug should be stopped if renal impairment develops and should not be used in the elderly (> 65 years). Other second generation Sulphonylureas (glimepiride, gliclazide and glipizide) may still be used with caution in these situations
- There is an apparent lower risk of hypoglycaemia with glimepiride and gliclazide MR

Caution:

- Sulphonylureas increase insulin secretion and therefore, increase the risk of hypoglycaemia. The risk is higher in renal impairment, liver cirrhosis and the elderly
- Sulphonylureas increase appetite and promote weight gain
- Sulphonylureas are contraindicated in patients known to be allergic to sulpha drugs
- Sulphonylurea drugs are highly protein bound. Administration of drugs that can displace them (e.g. NSAIDs, antithyroid drugs, sulpha drugs, anticoagulants and â-blockers) can increase the risk of hypoglycaemia
- All patients taking Sulphonylureas must be taught to recognize symptoms of hypoglycaemia and its management.

iii. Non Sulphonylureas (e.g. repaglinide, nateglinide)

- These are short acting insulin secretagogues which lower blood glucose acutely
- They are rapidly absorbed from the GI tract with a peak level 1-hour post administration and eliminated within 4 – 6 hours
- They should be taken within 10 minutes before main meals
- They can be combined with metformin, TZDs or α-glucosidase inhibitors, when indicated.

Dosage

Drug	Minimum Dose	Maximum Dose
Repaglinide	0.5 mg with main meals	4mg with main meals (not exceeding 16mg daily)
Nateglinide	60 mg with main meals	120mg with main meals (not exceeding 360mg daily)

Caution:

- There is a higher risk of prolonged hypoglycaemia with the combination of repaglinide and gemfibrozil[29]. This combination is contraindicated.

iv. α-glucosidase Inhibitors

- α-glucosidase inhibitors, e.g. acarbose, act at the gut epithelium, to reduce glucose absorption by inhibiting α-glucosidase enzymes. They should be taken with main meals.
- α-glucosidase inhibitors decrease postprandial glucose. They do not cause hypoglycaemia.
- They are particularly useful in postprandial hyperglycaemia. They can have synergistic effects when used with other Oral Anti-Diabetic Agents and may be combined with insulin.
- If hypoglycaemia occurs when used in combination with Sulphonylureas or insulin, advise patients to take monosaccharides, e.g. glucose.
- In patients with abnormal renal function, acarbose can be safely used. If diabetes is still not well controlled, insulin is required.

Dosage

Initial dose	50 mg/day and titrate accordingly
Usual dose	50-100 mg during main meals
Maximum dose	100 mg TDS

v. Thiazolidinediones (TZDs)

- Thiazolidinediones act primarily by increasing insulin sensitivity in muscle and adipose tissue and inhibit hepatic gluconeogenesis
- They act on the peroxisome proliferator-activated receptor-gamma (PPAR-γ) which regulates the transcription of insulin responsive genes and fatty acid metabolism
- Improvement in glycaemic control may only be seen after six weeks and maximal effect up to six months[30].
- They can be combined with other Oral Anti-Diabetic Agents (sulphonylureas or metformin) to improve glucose control, when indicated[12-15.]
- Side effects include weight gain, fluid retention, and haemodilution

Dosage

Drug	Minimum Dose	Maximum Dose
Rosiglitazone	4 mg OD	4 mg BD
Rosiglitazone and Metformin fixed combination	2 mg Rosiglitazone + 500 mg Metformin	4 mg Rosiglitazone + 500 mg Metformin
Pioglitazone	15 mg OD	45 mg OD

Note :

- Liver function tests must be monitored regularly every 6 – 8 weeks during the first six months of use

Caution :

- TZDs are contraindicated in patients with hepatitis, liver failure and congestive cardiac failure (NYHA Class III, IV)[31].

D. MONITORING

D1 SELF BLOOD GLUCOSE MONITORING

Self blood glucose monitoring (SBGM) is the method of choice in monitoring glycaemic control. SBGM is strongly advised for patients on insulin and is desirable for those on oral anti-diabetic agents (ADA, 2005)[32].

Frequency of blood glucose testing depends on the glucose status, glucose goals and mode of treatment.

Although home blood glucose monitoring has not been shown to have a significant impact on outcome measures such as HbA1c and body weight, it is recommended as part of a wider educational strategy to promote self-care. *[Grade C, Consensus]*

Monitoring provides information on the effects of therapy, diet and physical activity. Position Statement from ADA, 2005 recommends :

- SBGM should be carried out 3 or 4 times daily for patients using multiple insulin injections
- to achieve postprandial glucose targets, postprandial SBMG may be appropriate

Table 5: Recommendations for Self Blood Glucose Monitoring

Mode of Treatment	Breakfast		Lunch		Dinner	
	Pre	Post	Pre	Post	Pre	Post / Pre-bed
Diet Only	√	√		√		√
Oral anti-diabetic agent	√	√		√		√
Insulin #	√	√	√	√	√	√

Note:

√ Recommended timing of SBGM

√ Optional timing of SBGM

D1.1 Insulin Treated

Those on replacement insulin therapy need to check glucose levels before each meal and before bed (10 – 11 pm) (Refer to Targets for Control, page 8). On insulin therapy: pre-meal (breakfast, lunch, dinner) and pre-bed glucose levels (weekly-fortnightly). Once pre-meal glucose levels are achieved, PPG testing is recommended for fine-tuning of insulin dose. This information will allow adjustments of insulin dosage after taking into account the effect of diet and physical activity.

Interpretation of Glucose Monitoring in Relation to Insulin Therapy

Bedtime Insulin Daytime Sulphonylurea (BIDS)

Figure 1a: Bedtime Insulin Daytime Sulphonylurea – Intermediate Acting Insulin

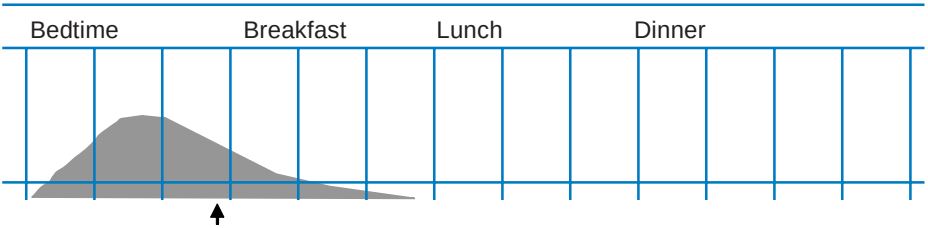
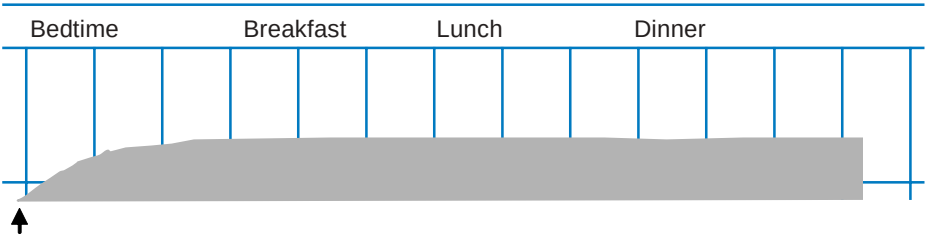


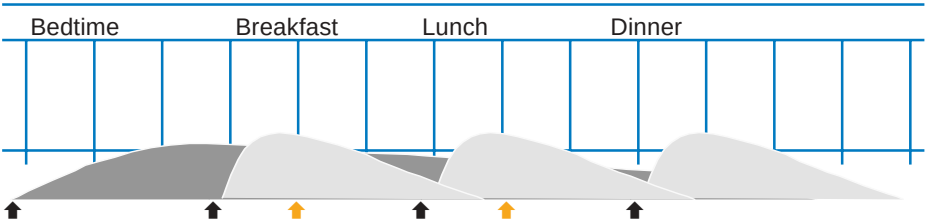
Figure 1b: Once Daily Basal Long Acting Insulin



- Values before breakfast give information about bedtime insulin (BIDS) (Refer to Figure 1a) or once daily basal long acting insulin (Refer to Figure 1b)

Basal Bolus Insulin Regimen

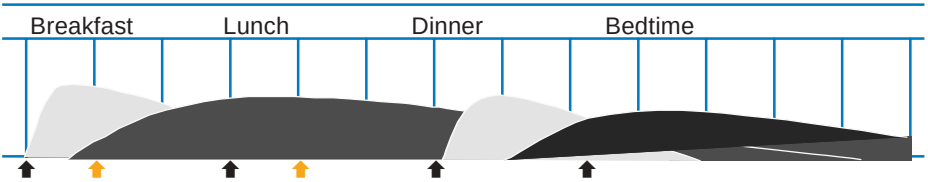
Figure 2: Basal Bolus Insulin Regimen



- Values before breakfast give information about pre-dinner or pre-bed intermediate acting insulin
- Insulin glargine may be used in place of NPH. It can be administered at any time of the day. Pre-breakfast values are used for dose titration
- Values before other main meals (pre-lunch or pre-dinner) reflect short acting insulin taken at the previous meal
- Once pre-meal glucose levels are achieved, PPG testing is recommended for fine-tuning of insulin dose (⬆Optional timing of SBGM)
- Values at pre-bed give information about short acting insulin given before dinner
- Rapid acting insulin analogues can be given in place of the short acting insulin. It should be given at the start or immediately after the meal. 2-hour PPG values are used for dose titration

Twice Daily Intermediate Acting with Short Acting Insulin

Figure 3: Intermediate Acting with Short Acting Insulin



- Values before breakfast give information about pre-dinner or pre-bed intermediate or long acting insulin
- Values at pre-lunch give information about short acting insulin given before breakfast
- Values at pre-dinner give information about the intermediate acting insulin given before breakfast
- Values at pre-bed give information about short acting insulin given before dinner
- Once pre-meal glucose levels are achieved, PPG testing is recommended for fine-tuning of insulin dose (⬆Optional timing of SBGM)

Ideally these tests should be done on a daily basis or if possible at least one 24–hour cycle per week.

Note

⬆ Recommended timing of SBGM

⬆ Optional timing of SBGM

D1.2 Diet or oral anti-diabetic agent

Those on tablets or diet need to check fasting and 2-hour PPG levels.

D2 HbA_{1c}

HbA1c should be measured approximately every 3 to 6 months to ensure that glycaemic targets are being met. *[Grade C, Consensus]*

This reflects overall glucose control over a 3 month period with recommended target level of 6.5% (IDF, 2003)[1].

Frequency of testing depends on availability. Ideally this should be every 3 – 6 monthly.

Recommendation : HbA1c Target

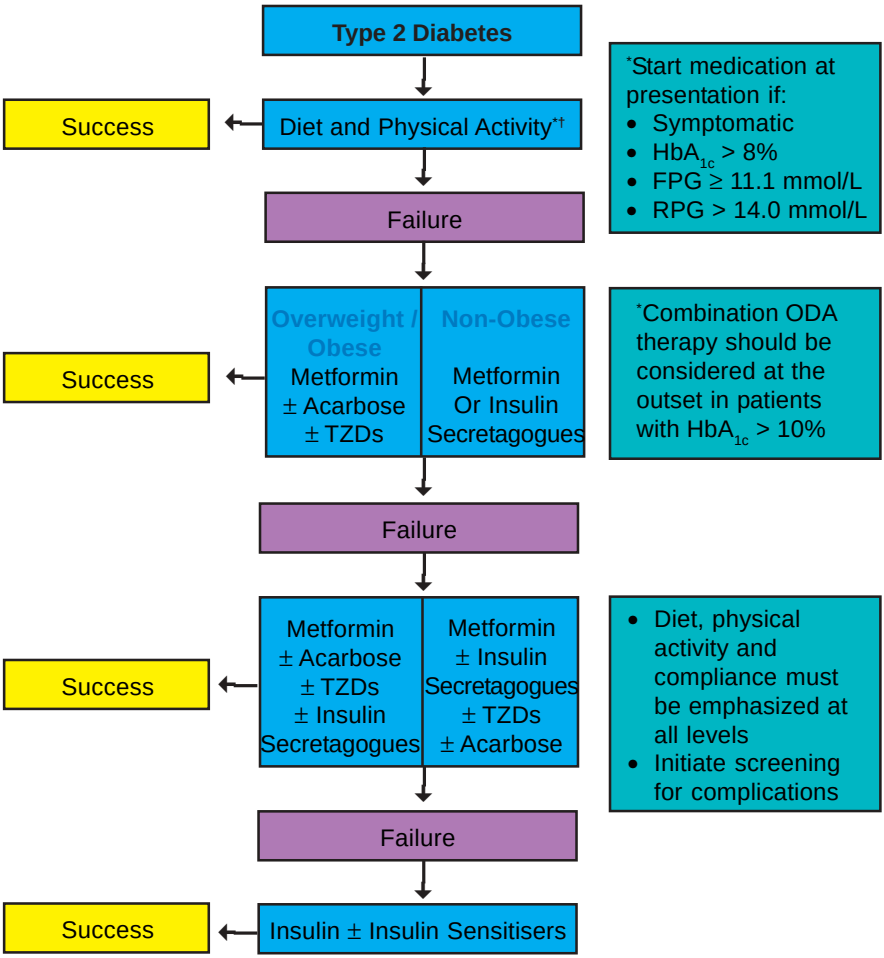
1. Glycemic targets must be individualized. Therapy in most patients with type 2 diabetes should be targeted to achieve an HbA1c < 6.5% in order to reduce the risk of microvascular *[Grade A[8]]* and macrovascular complications. *[Grade C, Consensus [2]]*

2. To achieve an HbA1c < 6.5%, aim for FPG or preprandial PG targets of 4.4 to 6.1 mmol/L and 2-hour postprandial PG targets of 4.4 to 8.0 mmol/L. *[Grade B[32]]*

D3 MONITORING OF OTHER RISK FACTORS

- Blood pressure and body weight should be monitored at each visit.
- Fasting lipids and urine for albuminuria / microalbuminuria need to be checked annually.
- If cardiovascular or renal complications are present or patients are on lipid-lowering and/or anti-hypertensive therapy, lipids and renal function may need to be checked more often.

Algorithm 4: Medication for Type 2 Diabetes



(NOTE: refer appendix 3 for types and dose of oral anti-diabetic agents and insulin [appendix C 1.3])

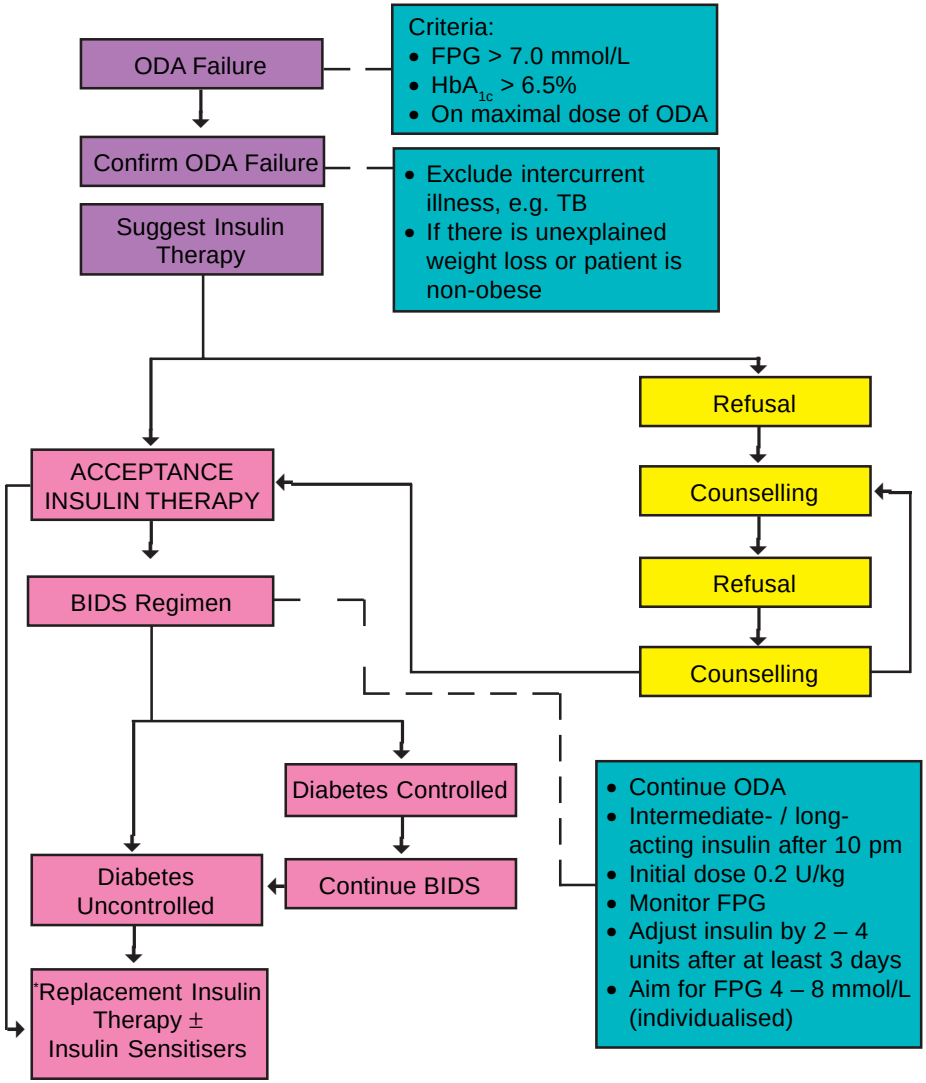
† *Trial of therapy with diet and physical activity alone should not exceed 3 months*

Caution:

Oral anti-diabetic agent must be used with care in:

- the elderly
- renal impairment
- liver cirrhosis

Algorithm 5: Oral Anti-Diabetic Agents Failure And Subsequent Insulin Therapy



*Note:

- As in Type 1, multiple insulin injections daily
- Monitor FPG, pre- and post-prandial levels, HbA_{1c}
- Adjust insulin doses accordingly

A1 DIABETES: THE DISEASE

a) It is a common chronic disorder
b) There is chronic hyperglycaemia together with other metabolic abnormalities
c) The role of insulin resistance and/or deficiency
d) Risk factors for cardiovascular disease
e) Currently there is no known cure but the disease can be controlled enabling the person to lead a healthy and productive life
f) Aim at reducing complication (micro & macro)

SYMPTOMS OF THE DIABETES

Fifty percent (50%) of patients are not aware that they have diabetes. The majority are asymptomatic.

A2.1 Acute Complications

a) Hypoglycaemia
b) Hyperglycaemia

Patients should be made aware of:

- Symptoms: Common symptoms include polyuria, polydipsia, tiredness and weight loss
- Precipitating factors (e.g. infection, intercurrent illness)
- Simple measures to avoid and manage the above

A2.2 Chronic Complications

a) Macrovascular
(e.g. Cardiovascular, Cerebral Vascular, Peripheral Vascular Systems)
b) Microvascular
(e.g. Nephropathy, Neuropathy and Retinopathy)

Inform patients regarding:

- Symptoms
- Preventive measures
- Coping strategies

A2.3 Lifestyle Measures

Diet and physical activity form an integral part of the management of diabetes. Education on lifestyle modification should be initiated at diagnosis and reinforced regularly.

A2.4 Medication

Emphasize that diet and physical activity are the mainstay of treatment. Medication should be given after an adequate trial of diet and physical activity, unless symptomatic or if the blood glucose remains high.

A2.5 Self-Care

Patients should be educated to practice self-care. This allows the patient to assume responsibility and control of his / her own diabetes management. Self-care should includes:

- Blood glucose monitoring
- Body weight monitoring
- Foot-care
- Personal hygiene
- Healthy lifestyle / diet or physical activity
- Identify targets for control
- Stop smoking

Table 6: Energy Expenditure

kcal/hr	Intensity	Types of Physical Activity
60	minimal	at rest
300	moderate	walking, gardening, unassisted golf
400	intermediate	cycling, swimming, tennis
600	strenuous	squash, running, hill climbing

Table 7: Types and Levels of Physical Activity

Level	Duration (min)	Types of Physical Activity
Mild	30	slow walking, shopping
Moderate	20	cycling at level surface, fast walking
Hard	10	climbing stairs or hills, jogging
Very Hard	5	soccer, swimming

Caution:

- Assess patients prior to recommending an exercise programme, with special attention to cardiovascular and neuropathic complications
- If blood glucose is $\geq$ 20 mmol/L, control diabetes first before starting exercise

General Guidelines for Use of Insulin in Diabetes

- β-cell failure in type 2 diabetes is mainly a clinical judgement
- Biochemical confirmation (e.g. glucagon stimulation test, insulin / C-peptide estimations) is not mandatory
- Treatment should be individualised taking into account concomitant medical problems and medications
- The combination of insulin and oral anti-diabetic agents can be used in oral anti-diabetic agent failure
- In the BIDS regimen, intermediate acting insulin should be given after 10 pm because of the risk of hypoglycaemia in the early hours of the morning. If insulin cannot be given after 10 pm, then it can be given in the morning before breakfast. Insulin glargine can be given at anytime of the day
- On insulin therapy: pre-meal (breakfast, lunch, dinner) and pre-bed glucose levels (weekly – fortnightly). Once pre-meal glucose levels are achieved, PPG testing is recommended for fine-tuning of insulin dose
- In the young, thin diabetic patient, replacement insulin therapy may be considered at the outset
- Choice of insulin formulations and/or combination regiments should be individualised
- Requirements of high dose of insulin should prompt a search for an underlying cause / secondary problems such as non-compliance, incorrect dosing and administration, occult infections and other aggravating factors
- Always be aware of episodic hypoglycaemia causing apparent poor diabetes control to avoid aggravating the problem
- All insulin treated patients must be taught basic survival skills
- All insulin treated patients must be encouraged to do self blood glucose monitoring (Refer to page 17)
- Onset of complications such as nephropathy or neuropathy is *not necessarily* an indication to commence insulin therapy
- Combination of TZD and insulin increases significant fluid retention. Caution should therefore be exercised.

Table 8: Human Recombinant Insulins and Analogues

Insulin Preparations	Onset of Action	Peak Action	Duration of Action
Fast Acting			
Rapid Analogue Aspart (Novorapid) Lispro (Humalog)	5 – 15 minutes	1 – 2 hours	4 – 6 hours
Human Regular Actrapid Humulin R	30 – 60 minutes	2 – 4 hours	6 – 10 hours
Intermediate Acting			
Human NPH Insulin Insulatard Humulin N	1 – 2hours	4 – 8 hours	10 – 16 hours
Long Acting			
Basal Long Acting Analogue Glargine (Lantus)	1 – 2 hours	Flat	~ 24 hours
Premixed Insulins			
Mixtard 20/80 Mixtard 30/70 Mixtard 50/50 Humulin 30/70 BIAsp 30/70	Biphasic onset and peak		10 – 16 hours

Note:
The time course of action may vary in different individuals, or at different times in the same individual. Because of these variations, time periods indicated above should be considered as general guidelines only. The higher the dose of the insulin, the longer is the duration of action.

Table 9 : Efficacy of the Different Types of Oral Anti-Diabetic Agents as Monotherapy[22]

Drug	Decrease in FPG (mmol/L)	1-hour PBG (↓ from baseline) (mmol/L)	HbA_{1c} (↓ from baseline) (%)
Sulphonylureas	2.2 – 3.3	-	1.0 – 2.0
Repaglinide / Nateglinide	1.7	3.1	1.1
Metformin	3.0	-	1.4
Rosiglitazone (across dose range)	1.4 – 3.0	-	0.1 – 0.7
Pioglitazone	1.1 – 3.0	-	0.3 – 0.9
α-glucosidase inhibitors	1.1 – 1.7	1.1 – 4.1	0.5 – 1.0

Oral Anti-Diabetic Agent	Levels of Evidence
Biguanides	I
Insulin Secretagogues –Sulphonylureas*	I and II
Insulin Secretagogues – Non-sulphonylureas	I
α-Glucosidase Inhibitor	I
TZD	I

*Note:

- Many of the older SUs (glibenclamide, gliclazide) have very limited evidence in terms of double-blind randomised control trials assessing their efficacy, therefore they only have level of evidence II. However, the UKPDS which had a large number of subjects and a long duration of study has demonstrated the efficacy of glibenclamide.
- The different insulin secretagogues appear to have comparable glucose lowering effects *(Level I)*[23]
- The newer SUs (glimepiride, nateglinide, repaglinide)[24,25] have similar glycaemic efficacy in head-to-head comparative trials with established older SUs (e.g. glibenclamide or glipizide)[26,27]

MANAGEMENT OF TYPE 2 DIABETES IN PREGNANCY

Women with type 2 diabetes who are planning pregnancy should be referred to the Physician / Diabetologist for further management.

Pre-Pregnancy:

- Counselling is important
- Pregnancy should be planned
- Achieve good glycaemic control before conception, aim for HbA_{1c} < 6.5%
- Insulin therapy may be necessary before conception

During Pregnancy:

- Achieve and maintain ideal glucose levels (Refer to Table 10)
- Close self blood glucose monitoring is required (individualize frequency of monitoring)
  - On diet therapy: pre-breakfast, 2-hour PPG levels (weekly – fortnightly)
  - On insulin therapy: pre-meal (breakfast, lunch, dinner) and pre-bed glucose levels (weekly – fortnightly). Once pre-meal glucose levels are achieved, PPG testing is recommended for fine-tuning of insulin dose
- Fructosamine (fortnightly)
- HbA_{1c} (4 – 6 weekly)
- Insulin therapy is indicated when diet fails. Oral Anti-Diabetic Agents are not recommended
- GIK (Glucose-Insulin-Potassium) regimen can be used during delivery / LSCS

Post-partum:

- Insulin requirement drops immediately after delivery by 60 – 75%
- In breast-feeding, if glycaemic control is inadequate with diet alone, insulin should be continued at a lower dosage

Table10 : Targets for Pregnant Women

Timing	Glucose Levels (mmol/l)
Pre-breakfast	3.5 – 5.3
Pre-prandial	3.5 – 5.8
2-hour postprandial	4.4 – 6.7
0200 – 0400 Hours	> 3.9

MANAGEMENT OF TYPE 2 DIABETES IN ACUTE ILLNESS, SURGERY, STRESS AND EMERGENCIES:

- Oral anti-diabetic agent may not be adequate in maintaining euglycaemia during stress and emergency situations (e.g. infection, myocardial infarction and surgery)
- In any form of stress, if glycaemic control is inadequate, oral anti-diabetic agent therapy should be replaced by insulin
- DKA may develop during stress
- Oral anti-diabetic agent regimen may be resumed when stress has resolved
- If the patient develops DKA during stress and the patient is young, consider long-term insulin therapy

Table 11 : Management of Diabetes During Stress and Emergency Surgery

Status of Control	Minor Surgery	Major Surgery
Acceptable Control FPG < 8.0 mmol/L RPG < 11.0 mmol/L	• Stop Oral Anti-Diabetic Agent • Resume Oral Anti-Diabetic Agent post-op, once taking orally	• Stop Oral Anti-Diabetic Agent • GIK regimen during op • s/c insulin post-op, once taking orally
Poor Control FPG ≥ 8.0 mmol/L RPG ≥ 11.0 mmol/L	• Stop Oral Anti-Diabetic Agent • GIK regimen (pre- and intra-op) • s/c insulin post-op, once taking orally	

- If elective surgery, delay operation until glycaemic control is achieved. Control with insulin or Oral Anti-Diabetic Agent as indicated
- GIK regimen[39] can be continued until food intake after surgery
- Maintain insulin therapy post-surgery until stress is resolved and satisfactory wound healing is achieved

SECTION 3 MANAGEMENT OF CHRONIC COMPLICATIONS

3.1 INTRODUCTION

- Type 2 diabetes patients should be screened for complications at diagnosis and thereafter at yearly intervals [35](*ADA, 2005*)
- The UKPDS data confirmed that in Type 2 diabetes, improvement of glycaemic control by lowering of the HbA_{1c} lowers the risk of developing both macrovascular and microvascular complications [36], [37](UKPDS. 1998)

3.2 DETECTION AND TREATMENT OF DIABETES COMPLICATIONS

Microvascular complications

i. Retinopathy
(Refer to Clinical Practice Guidelines: Diabetic Retinopathy, 1996)

ii. Nephropathy
(Refer to Clinical Practice Guidelines: Management of Diabetic Nephropathy, 2004)

iii. Neuropathy

Macrovascular complications

iv. Ischaemic heart disease
(Refer to Clinical Practice Guidelines on Acute Myocardial Infarction, 2001; Clinical practice Guidelines on Unstable Angina, 2002; Clinical practice Guidelines on Heart Failure, 2000)

v. Cerebrovascular disease
(Refer to Consensus Statement on The Management of Ischaemic Stroke, 2000)

vi. Peripheral vascular disease
(Refer to Clinical Practice Guidelines: Management of Diabetic Foot, 2004)

Combination of Micro- and Macrovascular complications

vii. Diabetic Foot
(Refer to Clinical Practice Guidelines: Management of Diabetic Foot, 2004)

viii. Erectile Dysfunction
(Refer to Clinical Practice Guidelines on Erectile Dysfunction, 2000)

[Note: The above guidelines are also available electronically at the following websites: www.moh.gov.my; www.acadmed.org.my;]

Currently there is no practice guideline available on diabetes neuropathy, and peripheral vascular disease.

NEUROPATHY

Patients should be made aware of the significance of absence or decrease of pain sensation and pulse of feet/hands. Those with significant altered sensation and absence of pulses are at high risk of amputations.

Patients with long standing or poorly controlled diabetes should be made aware of the possibility of autonomic dysfunction which may present with symptoms such as postural giddiness, postprandial fullness, diarrhoea, abnormal sweating and in males there is possibility of erectile dysfunction (ED).

Screening for peripheral neuropathy should be carried out at diagnosis and annually to identify those at high risk of developing foot ulcers (ADA, 2005).

Neurological assessment of lower limbs

Assessment should include at least one of the following:

- Vibration sense with 128 cycle tuning fork[38] (Meijer et al, 2005)
- Touch sensation using 10 g monofilament[39] (Pham H et al, 2000)

Assessment for autonomic neuropathy (Refer Appendix 3a)

Treatment

- Those with significant chronic disturbing pain in their feet may be considered for the following drugs: amitriptyline, carbazepine, gabapentin [40](Boulton, 2005), [41](Max MB, 1987) [42](Backonja et al, 1998)
- Those with high risk feet (i.e. loss of pain sensation, absence foot pulses and deformities) should be managed as according to CPG on Management of Diabetic Foot, 2004
- Educate on appropriate footwear to prevent callus formation or ulceration/blisters forming
- Strict glycaemic control should be considered to prevent the onset and progression of neuropathy. [43]*[UKPDS, 1998, Grade B]*

DIAGNOSIS OF AUTONOMIC NEUROPATHY [44]

PARASYMPATHETIC DAMAGE

1. Heart-rate response to Valsalva manoeuvre
   - Patient sitting, with continuous ECG recording
   - Blow into anaeroid manometer at 40 mm Hg for 15 secs at 1 min intervals x 3
   - Mark on ECG recording blow and release
   - Measure longest and shortest R-R interval (mean of 3)
   - Contraindicated in presence of proliferative retinopathy

   Result:
   - Normal: > 1.21
   - Abnormal: < 1.10

2. Heart rate response to deep breathing
   - Patient sitting, with continuous ECG recording
   - 6 deep breaths in 1 min (10 seconds per cycle)
   - Measure max and min HR (mean of 6), variation = max - min HR or RR interval expiration/ inspiration = E/I ratio

   Result:
   - Normal: max - min = 15 beats/min or E/I ratio > 1.21
   - Abnormal: max - min = < 10 beats/min or E/I ratio < 1.10

3. Immediate heart rate response to standing
   - Lie patient on couch, ECG recording, mark time patient stands
   - Measure RR interval at around 30th beat (longest) and 15th beat (shortest)

   Result:
   - Normal: RR 30/RR 15 > 1.04
   - Abnormal: RR 30/RR 15 < 1.00

SYMPATHETIC DAMAGE

4. Blood pressure response to standing
   - Record drop in systolic BP on standing from lying position

   Result:
   - Normal: difference in systolic BP < 10 mm Hg
   - Abnormal: difference in systolic BP > 30 mm Hg

5. BP response to handgrip
   - Patient sitting
   - Measure baseline BP x 3 and calculate mean baseline diastolic BP
   - Patient to grip a handgrip dynamometer or sphygmomanometer record maximal handgrip (mm Hg)
   - Ask patient to grip at 30% of maximal handgrip for up to 5 minutes
   - Measure BP at 1 min interval x 5
   - Highest diastolic BP - mean baseline diastolic BP

   Result:
   - Normal: > 16 mm Hg
   - Abnormal: < 10 mm Hg

SECTION 4 PREVENTION OF TYPE 2 DIABETES MELLITUS

For healthy and people with risk

There are many risk factors that predispose an individual or population to developing diabetes. Besides genetic, there is ample evidence to show that the main factor influencing the explosion of diabetes in modern times is lifestyle related changes. As diabetes is an endpoint in the glucose tolerance continuum in a general population, it is possible to halt this slide from normal to impaired glucose tolerance (IGT) and subsequently type 2 DM.

Prediabetes

There is evidence showing that interventions to improve insulin sensitivity can bring about a reduction in the conversion of IGT to frank type 2 DM.

- Diet and physical activity[45], [46], [47]
- Metformin[48]
- Acarbose[49]
- Orlistat[50]
- Troglitazone[51]

It must be emphasised that while pharmaceutical intervention is available, lifestyle intervention programmes have greater efficacy[1] and practical and cost effective making its implementation possible in any primary health care setting[1-7]. Longstanding positive behavioural adaptation and lifestyle modification will provide the answers to our fight against the impending epidemic of type 2 DM.

Recommendation : Prevention of Type 2 Diabetes Mellitus

1. In individuals with IGT, a structured program of lifestyle modification that includes moderate weight loss and regular physical activity has been shown to reduce the risk of type 2 diabetes. *[Grade* A[52], [53]*]*

2. In individuals with IGT, pharmacologic therapy with metformin (biguanide) *[Grade A[9]]* or acarbose (alpha-glucosidase inhibitor) *[Grade A[54]] can* be considered to reduce the risk of type 2 diabetes.

REFERENCES:

1. International Diabetes Federation (IDF) (European Region), Brussels. Guidelines for type 2 Diabetes Mellitus. *Diabetic Medicine*. 1999;16(9):716-30.
2. Global Guideline for Type 2 Diabetes, International Diabetes Federation, 2005
3. American Diabetes Association. Clinical Practice Guideline 2004
4. Malaysian Clinical Practice Guidelines on the Management of Obesity, 2003
5. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure JNC VII.
6. Malaysian Clinical Practice Guidelines: Management of Diabetic Nephropathy, 2004
7. Colagiuri S, Miller JJ, Edwards RA. Metabolic effects of adding sucrose and aspartame to the diet of subjects with non-insulin-dependent diabetes mellitus. *Am J Clin Nutr.* 198;50:474-8.
8. Chantelau EA, Gösseringer G, Sonnenberg GE, et al. Moderate intake of sucrose does not impair metabolic control in pump-treated diabetic out-patients. *Diabetologia.* 1985;28:204-7.
9. UK Prospective Diabetes Study (UKPDS) 33 Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications inpatients with type 2 diabetes. *Lancet.* 1998;352:837-53.
10. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet.* 1998;352"854-65.
11. Aronoff S, Rosenblatt S, Braithwaite S, et al. Pioglitazone hydrochloride monotherapy improves glycaemic control in the treatment of patients with type 2 diabetes: a 6-month randomized placebo-controlled dose-response study. They Pioglitazone 001 Study Group. *Diabetes Care.* 2000;23(11):1605-11.
12. Lebovitz HE, Dole JF, Patwardhan R, et al. For the Rosiglitazone Clinicals Trials Group. Rosiglitazone monotherapy is effective in patients with type 2 diabetes. *J Clin Endocrinol Metab.* 2001;86:280-8.
13. Lebovitz HE, Dole JF, Patwardhan R, et al. For the Rosiglitazone Clinicals Trials Group. Rosiglitazone monotherapy is effective in patients with type 2 diabetes. *J Clin Endocrinol Metab.* 2001;86:280-8.
14. Jones TA, Saulter M, Van Gaal LF, Jones NP. The addition of rosiglitazone to metformin is most effective in obese, insulin resistant patients with type 2 diabetes. *Diabetes Obes Metab.* 2003;5:163-70.

15. Fonseca V, Rosenstock J, Patwardhan R, et al. Effect of metformin and rosiglitazone combination theapy in patients with type 2 diabetes: a randomized control study. *JAMA*. 2000;283:1695-702.

16. Hanefeld M, Brunetti P, Guntram H, et al. One year glycaemic control with sulphonylurea plus pioglitazone versus a sulphonylurea plus metformin in patients with type 2 diabetes. *Diabetes Care.* 2004;27:141-7.

17. Lebovitz HE, Benerji MA. Insulin resistance and its treatment with thiazolidinediones. *Recent Prog Horm Res.* 2001;56:265-94.

18. Staged Diabetes Management – A Systematic Approach, International Diabetes Center, 2000.

19. Pugh JA, Wagner ML, Sawyer J, et al. Is combination sulphonylurea an insulin therapy useful in NIDDM patients? *Diabetes Care.* 1992;15:953-8.

20. Yki-Järvinen H, Ryysy L, Nikkilä K, et al. Comparison of bedtime insulin regimens in patients with type 2 diabetes mellitus. A randomized, controlled trial. *Ann Intern Med*. 1999;130:389-396.

21. Ponssen HH, Elte JWF, Lehert P, et al. Combined metformin and insulin therapy for patients with type 2 diabetes mellitus. *Clin Ther.* 2000;22:709-18.

22. Avilés-Santa L, Sinding J, Raskin P. Effects of metformin in patients with poorly controlled, insulin-treated type 2 diabetes mellitus. A randomized, double-blind, placebo-controlled trail. *Ann Intern Med.* 1999;131:182-8.

23. Wright A, Burden ACF, Paisey RB, et al. Sulphonylurea inadequacy: efficacy of addition of insulin over 6 years in patients with type 2 diabetes in the U.K. Prospective Diabetes Study (UKPDS 57). *Diabetes Care.* 2002;25:330-6.

24. Raskin P, Rendell M, Riddle MC, et al. A randomized trial of rosiglitazone therapy in patients with inadequately controlled insulin-treated type 2 diabetes. *Diabetes Care.* 2001;24:1226-32.

25. Chiasson J-L, Josse RG, Hunt JA, et al. The efficacy of acarbose in the treatment of patients with non-insulin-dependent diabetes mellitus. A multicenter controlled clinical trial. *Ann Intern Med.* 1994;121:928-35.

26. Coniff RF, Shapiro JA, Seaton TB, et al. A double-blind placebo controlled trial evaluating the safety and efficacy of acarbose for the treatment of patients with insulin-requiring type II diabetes. *Diabetes Care.* 1995;18:928-32.

27. UK Prospective Diabetes Study (UKPDS) 33 Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications inpatients with type 2 diabetes. *Lancet.* 1998;352:837-53.

28. American Diabetes Association (ADA). Position Statement. *Diabetes Care* 2003:26 (Suppl 1).

29. Niemi M, Blackman JT, Neuvonen M, Neuconen PJ. Effects of gemfibrosil, itraconazole and their combination on the pharmacokinetics and pharmacodynamics of repaglinide: potentially hazardous interaction between gemfibrosil and repaglinide. *Diabetologia* 2003;46(3):347-351.

30. Lebovitz HE, Benerji MA. Insulin resistance and its treatment with thiazolidinediones. *Recent Prog Horm Res.* 2001;56:265-94.

31. Nesto RW, Bell D, Bonow RO, Fonseca V, et al. Thiazolidinedione use, fluid retention and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association. *Diabetes Care.* 2004;27:256-63.

32. American Diabetes Association (ADA). Position Statement 2005

33. Global Guideline for Type 2 Diabetes, International Diabetes Federation, 2005

34. Stratton IM, Adler AI, Neil HAW, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ*. 2000;321:405-412.

35. American Diabetes Association Position Statement 2005, Diabetes Care, Vol 28, Supp1, Jan 2005.

36. UK Prospective Diabetes Study (UKPDS) Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 352: 837-853, 1998.

37. UK Prospective Diabetes Study (UKPDS) Group: Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 352:854–865, 1998

38. Back to Basics in Diagnosing Diabetic Polyneuropathy With the Tuning Fork, Meijer et al, Diabetes Care. 28(9):2201-2205, September 2005.

39. Screening Techniques to Identify People at High Risk for Diabetic Foot Ulceration: A Prospective Multicenter Trial. Pham H, Armstrong DG, Harvey C, Harkless LB, Giurini JM, Veves A *Diabetes Care* 2000 May;23(5):606-11.

40. Management of Diabetic Peripheral Neuropathy. Andrew J.M. Boulton,, Clinical Diabetes, Volume 23, Number 1, 2005.

41. Max MB, Culnane M, Schafer SC, et al. Amitriptyline relieves diabetic neuropathy pain in patients with normal or depressed mood. *Neurology*. 1987;37:589-596.

42. Backonja M, Beydoun A, Edwards KR, et al. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. *JAMA*. 1998;280:1831-1836.

43. UK Prospective Diabetes Study (UKPDS) 33 Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications inpatients with type 2 diabetes. *Lancet.* 1998;352:837-53.

44. Ewing DJ, Clarke BF. Diagnosis and management of diabetic autonomic neuropathy. *Br Med J (Clin Res Ed).* 1982;285(6346):916-8.

45. The Diabetes Prevention Program Research Group. Reducation in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med.* 2002; 346:393-403.

46. Pan XR, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. *Diabetes Care.*1997 Apr;20(4):537-44.

47. Lindstrom J, Tuomilehto J. The diabetes risk score: A practical tool to predict type 2 diabetes risk. *Diabetes Care.* 2003;26(3):725-31.

48. The Diabetes Prevention Program Research Group. Reducation in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med.* 2002; 346:393-403.

49. Chiasson JL, Gomis R, Hanefeld M, Josse RG, Karasik A, Laakso M. The STOP-NIDDM Trial: an international study on the efficacy of an alpha-glucosidase inhibitor to prevent type 2 diabetes in a population with impaired glucose tolerance: rationale, design, and preliminary screening data. Study to Prevent Non-Insulin-Dependent Diabetes Mellitus. *Diabetes Care.* 1998;21(10):1720-5.

50. Torgerson JS, Hauptman J, Boldrin MN, Sjostrom L. Xenical in the prevention of Diabetes in Obese Subjects (XENDOS) Study: A randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 in obese patients. *Diabetes Care.* 2004;27(1):155-61.

51. Azen SP, Peters RK, Berkowitz K, Kjos S, Xiang A, Buchanan TA. TRIPOD (Troglitazone In the Prevention Of Diabetes): a randomized, placebo-controlled trial of troglitazone in women with prior gestational diabetes mellitus. *Control Clin Trials.* 1998;19(2):217-31.

52. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet.* 1998;352"854-65.

53. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346:393-403.

54. Chiasson J-L, Josse RG, Gomis R, et al. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomized trial. *Lancet*. 2002;359:2072-2077.

GLOSSARY OF TERMS:

ACEI	Angiotensin Converting Enzyme Inhibitor
ADA	American Diabetes Association
AER	Albumin Excretion Rate
ARB	Angiotensin II Receptor Blocker
BD	Twice Daily (*Bis Die*)
BIDS	Bedtime Insulin Daytime Sulphonylurea
BMI	Body Mass Index
BP	Blood Pressure
BUSE	Blood Urea and Serum Electrolyte
CCF	Congestive Cardiac Failure
CVD	Cardio Vascular Disease
CXR	Chest X-Ray
DCCT	Diabetes Control and Complications Trial
DKA	Diabetes Ketoacidosis
DM	Diabetes Mellitus
E/R	Expiration/Inspiration Ratio
ECG	Electro Cardiogram
ED	Erectile Dysfunction
FBG	Fasting Blood Glucose
FPG	Fasting Plasma Glucose
GIK	Glucose Insulin Potassium
HbA_{1c}	Glycosylated Haemoglobin
HDL	High Density Lipoprotein
HR	Heart Rate
IDF	International Diabetes Federation
IFG	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance
LDL	Low Density Lipoprotein
LSCS	Lower Segment Caesarean Section
NCEP	National Cholesterol Education Program
NPH	Neutral Protamine Hagedorn
NSAIDs	Non-steroidal Anti-imflammatory Drugs
NYHA	New York Heart Association
OD	Once Daily (*Omni Die*)
ODA	Oral Anti-diabetic Agents
OGTT	Oral Glucose Tolerance Test
OM	On Morning (*Omni Mane*)
ON	On Night (*Omni Nocte*)
PPAR-ã	Peroxisome Proliferator-Activated Receptor-Gamma
PBG	Post-prandial Blood Glucose
PPG	Post-prandial Plasma Glucose
RPG	Random Plasma Glucose
S/C	Subcutaneous

SBMG	Self Blood Monitoring Glucose
SIADH	Syndrome of Inappropriate ADH
SU	Sulphonylurea
TB	Tuberculosis
TDS	Three Times Daily (*Ter Die Sumendus*)
TZD	Thiazolidinedione
UKPDS	United Kingdom Prospective Diabetes Study
UTI	Urinary Track Infection
WC	Waist Circumference
WHO	World Health Organisation
WHR	Waist Hip Ratio