

# Everyday Practice: Diabetes Mellitus

## Insulin therapy for patients with type 2 diabetes mellitus

NISHA R. S., E. BHATIA

### INTRODUCTION

India has the largest number of patients with type 2 diabetes mellitus (T2DM) in the world. It is estimated that currently their number is nearly 40 million, and will reach 70 million by the year 2025. It is not commonly realized by patients as well as physicians that T2DM is a progressive disease. Even at the time of diagnosis of diabetes, the  $\beta$ -cell reserve is diminished to nearly 50%, and this falls further with increasing duration of diabetes. It is estimated that over time more than half of the individuals with diabetes will require insulin.

Whenever it is required for achieving glycaemic control, the institution of insulin treatment should not be delayed. If hyperglycaemia is uncontrolled despite an adequate diet, exercise and maximum doses of 2 (or at the most 3) oral hypoglycaemic agents (OHA), then insulin is essential. Insulin therapy decreases plasma glucose levels by reducing hepatic glucose production and by increasing uptake of glucose into the muscle. It also improves insulin secretion by reducing 'glucotoxicity', i.e. the reversible impairment of  $\beta$ -cell function induced by high glucose levels. In the long term, good glycaemic control reduces the risk of chronic microvascular complications of diabetes and may reduce the risk of cardiovascular disease. This has been well demonstrated by many studies including the United Kingdom Prospective Diabetes Study (UKPDS) and the Kumamoto trial.

Unfortunately, initiation of insulin therapy is often delayed in patients with uncontrolled hyperglycaemia. Both patients and physicians perceive insulin therapy as too complex to manage. Most patients believe that the use of insulin is associated with advanced stages of diabetes and are uncomfortable with the thought of taking insulin injections lifelong. Various beliefs (fear of injections, weight gain and hypoglycaemia) need to be addressed through patient education.

In this article we discuss the use of insulin in patients with T2DM, with an emphasis on a practical scheme for insulin use in the Indian context. Presented first is a section on insulin, its types, profile of action, storage, side-effects and costs. This is followed by a description of the actual steps of its use in T2DM, including how to monitor glycaemic control, determine if insulin is required, insulin regimens, initiate insulin therapy and day-to-day insulin adjustments.

### INSULINS AND THEIR PRACTICAL USE

#### Insulins available in India

The different types of insulin and their action profile are shown in Table I and Fig. 1. It is important to note the following points:

Sanjay Gandhi Postgraduate Institute of Medical Sciences, Rae Bareilly Road, Lucknow 226014, Uttar Pradesh, India

NISHA R. S., E. BHATIA Department of Endocrinology

Correspondence to E. BHATIA; [ebhatia@sngpi.ac.in](mailto:ebhatia@sngpi.ac.in)

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1. Insulins from animal sources are now not freely available in India.
2. Lente insulin is no longer available in India.
3. Regular insulin needs to be injected 30 minutes before a meal; it is used to control meal-related glucose excursions.
4. Neutral protamine Hagedorn (NPH) insulin has a duration of action of 10–14 hours; it has a broad peak at 4–8 hours; it is used to provide basal insulin (at night) as well as prandial insulin (covering lunch, when given before breakfast).

*Premixed insulins.* Various premixed insulin preparations are available. These are popular because of the practical advantages

TABLE I. Types of insulin available in India and their action

Insulin type	Onset of action	Peak of action	Duration of action
<i>Rapid-acting analogues</i>			
Lispro or aspart	5–15 minutes	60–90 minutes	3–4 hours
<i>Short-acting</i>			
Regular/soluble	0.5–1 hours	2–4 hours	5–8 hours
<i>Intermediate-acting</i>			
NPH	2–4 hours	4–8 hours	10–14 hours
<i>Long-acting</i>			
Glargine	2–4 hours	Peakless	20–24 hours
Detemir	0.8–2 hours	3–9 hours (peak not pronounced)	Up to 24 hours
<i>Premixed</i>			
70% NPH/ 30% regular	30–60 minutes	Dual	16 hours
75% NPH/ 25% lispro	5–15 minutes	Dual (1–6.5 hours)	10–16 hours

NPH neutral protamine Hagedorn

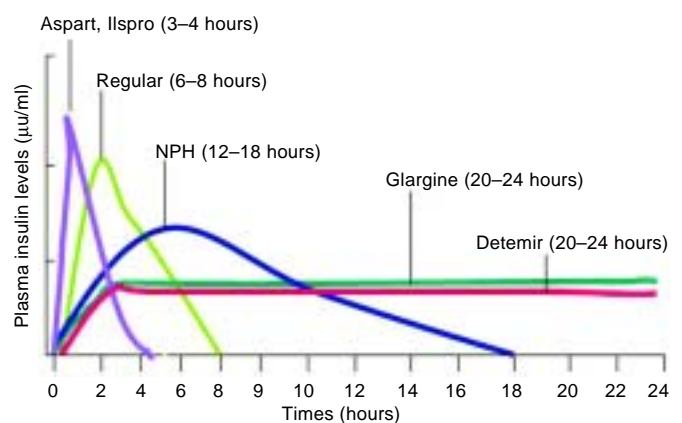


FIG 1. Activity profile of various insulins. The duration of insulin action is given in brackets.

of covering both basal and prandial (meal-related) insulin needs with a single preparation. Premixed preparations most often contain short-acting and intermediate-acting insulin (70% NPH and 30% regular insulin). These have the advantage of convenience and are especially helpful in individuals who have difficulty in drawing insulin from two different bottles. They have the disadvantage that the short- and intermediate-acting insulins are in a fixed proportion, which may not be suitable for achieving optimal glycaemic control in all patients. In addition, adjusting the insulin dose is difficult. Mixtures containing newer rapidly-acting analogues are also available (Table I). They are more convenient since insulin can be taken just before a meal. However, they offer little other advantage and add substantially to the expense.

**Insulin analogues.** These are modified insulins which have some advantages compared to conventional (regular and NPH) insulins. These offer greater convenience and can result in a decrease in the frequency of hypoglycaemia (at night and between meals). However, they often do not lead to improvement in glycaemic control. Rapid-acting analogues lispro and aspart can be injected just before a meal. Long-acting analogues (detemir and glargine) act for 24 hours and have peakless action. The cost of insulin analogues is nearly 3–8 times higher than that of conventional insulins.

#### Strength

Insulins are available in 2 strengths: 40 units/ml and 100 units/ml. The 100 units/ml strength should be used whenever the insulin dose at one time exceeds 40 units. It is very important to inform the patient that separate syringes are to be used for different strengths (U-40 syringes deliver U-40 insulin and U-100 syringes deliver U-100 insulin) and they cannot be mixed.

#### Timing of the doses of insulin

Basal insulins (e.g. NPH, detemir, glargine) are administered once or twice daily, usually before dinner or at bedtime. The timing of bolus insulins varies according to the onset of action. Rapid-acting insulin analogues (lispro, aspart) can be administered immediately prior to a meal, while regular insulin must be administered at least 30 minutes before a meal.

#### Insulin delivery systems

These include disposable insulin syringes and insulin 'pens'. Syringes have the advantage of being cheaper. They also allow 2 types of insulins (e.g. regular and NPH) to be mixed in different proportions. Syringes are marked as 40 units/ml or 100 units/ml and have to be used with the correct strength of insulin. Insulin 'pens' are convenient and easier to use than syringes. However, the insulin cartridges used in these are more expensive and do not allow two insulins to be mixed in different proportions. There are certain situations in which pens are very useful. In patients with visual impairment they allow the patient to measure the dose by listening to the number of 'clicks'. In addition, insulin pens are

very convenient for those who need to inject insulin at work or during travel.

#### Mixing of insulin

When a mixture of two insulins is drawn up, clear insulin (short-acting) is drawn before cloudy insulin (intermediate- or long-acting). Insulins from different manufacturers should not be used together. Rapid-acting insulin analogues can be mixed in the same syringe as NPH insulin. However, insulin glargine or detemir should not be mixed with any other type of insulin.

#### Injection sites

Insulin should be injected into the subcutaneous tissue. It is preferable, though not essential, to clean the skin prior to injection. Injection sites include the front or lateral aspect of the thigh, abdomen (absorption is faster than in the thigh and less affected by muscle activity during exercise), buttocks (upper outer quadrant) or lateral aspect of the arm (needs to be given by an attendant). Insulin should never be injected into the forearm or calves. It is advisable to practise rotating the sites with each injection.

#### Storage and safety

Insulin should not be stored in the freezer, in direct sunlight or in the glove compartment of a car. Opened insulin can be stored at room temperature in winters but it is best to store it in a refrigerator in the summer months. If refrigeration is not available, one can use a cooling jar or place a cool wet cloth around the insulin. After opening, the vial should be discarded in 3 months if kept at 2–8 °C or after 1 month if kept at room temperature. Regular insulin, aspart, lispro, glargine and detemir solutions are clear and should be discarded if these have particles or they become discoloured. NPH insulin should not have any small particles or clumps and should form a suspension easily. Patients should always buy insulin with a long expiry date and from a reliable pharmacy.

#### Side-effects of insulin

**Local effects.** Infection or local hypersensitivity at the injection site is uncommon. In contrast, lipohypertrophy or the accumulation of fat and fibrous tissue in lumps underneath the skin is common. In addition to being unsightly, there is poor absorption from these sites.

**Hypoglycaemia.** In general, severe hypoglycaemia (seizures, coma or any episode needing assistance) is less common than in type 1 diabetes. Insulin doses often do not fluctuate in patients with T2DM and hypoglycaemia is uncommon. The main causes of hypoglycaemia are missed or delayed meals, excessive exercise and inadvertent increase in insulin doses. In patients with T2DM with renal failure, hypoglycaemia is very common and the doses of insulin need to be substantially decreased.

**Weight gain.** This is a common problem and ranges from 2 to 4 kg. It occurs mainly due to a reduction in glycosuria. Patients should be advised to strictly adhere to the diet schedule and take regular exercise to minimize this side-effect. In some cases, concomitant use of metformin with insulin leads to a lesser weight gain.

#### Cost

The cost of insulin analogues is approximately 3–8 times that of regular/NPH insulins. For a patient injecting 30 units NPH and 30 units regular insulin daily, the monthly cost of the insulin and syringes is Rs 1200–1500. The cost will be close to Rs 2100 per

TABLE II. Targets for glycaemic control recommended by the American Diabetes Association, 2007

Parameter	Target
Fasting or pre-meal glucose	90–130 mg/dl
Post-meal glucose	<180 mg/dl
Haemoglobin A1c*	<7%

\* Normal levels of haemoglobin A1c are 4%–6%

month if one is using these preparations with a pen device. For a regimen containing glargine/detemir and lispro/aspart, the monthly cost of insulin and needles will range from Rs 4000 to Rs 4500.

**STEPS OF INSULIN THERAPY**

*Monitoring glycaemic control*

To decide the type of treatment required, glycaemic control needs to be closely monitored. A simple way of doing this is to accurately measure body weight; progressive loss of weight is an important indicator of poor glycaemic control. Elevated plasma glucose (fasting and pre-meals >130 mg/dl, 2 hours post meal >180 mg/dl) on 2 or more occasions implies poor control. The most important test is the haemoglobin A1c (HbA1c), which reflects the average plasma glucose levels over the previous 3 months. The normal range for most assays is 4%–6%; a value <7% implies good control while a higher value means that further action is required (Table II). In patients who are in good control, HbA1c can be measured 6-monthly, while in those whose control is poor, 3-monthly monitoring is required.

*Determine if insulin is required*

Insulin may be needed on a temporary or permanent basis (Table III). In general, in a well controlled patient, insulin may be required on a temporary basis at a time of intercurrent illness, stress or during pregnancy. Much more common is the situation where insulin is required on a permanent basis. Most commonly, patients after being managed for a variable number of years with OHA, fail to maintain adequate glycaemic control (HbA1c >7%). In rare instances, patients with type 1 diabetes (severe hyperglycaemia, weight loss, large amount of urine ketones) may present in adulthood and require insulin from the time of diagnosis.

In clinical practice, the most common situation that arises is failure of control of plasma glucose while the patient is already on OHA. It is useful to remember that an OHA will bring down the HbA1c by approximately 1%–2% (average of 40–80 mg/dl glucose). Hence, when a patient on OHA has an HbA1c between 7% and 10%, the addition of a second (or occasionally third) OHA with a different mode of action is likely to be useful. However, with an HbA1c >10%, insulin is the best option for achieving adequate control, even if the patient is only on a single OHA (Table IV).

*Insulin regimens*

There are many regimens (Table V, Fig. 2) and it is best to be familiar with only a few insulins and regimens. The regimen is decided by the degree of hyperglycaemia, the education and motivation level of the patient, economic status and presence or absence of complications.

**Basal insulin regimen.** When starting patients who are on OHA on insulin, in those with an HbA1c of 7%–9% (patients who have predominantly fasting hyperglycaemia), a simple approach is to start with a single injection of basal insulin at bedtime and to continue the OHA during the daytime. Either NPH or glargine/detemir insulin may be used. This schedule reduces fasting hyperglycaemia and is convenient for the patient.

**Split-mix insulin.** If glycaemic control on OHA is very poor (HbA1c >10%), or if the basal insulin fails to achieve the glycaemic target (HbA1c <7%), then split-mix insulin should be started. This consists of twice daily regular and intermediate insulin. Sulphonylureas are stopped when such a schedule is initiated but metformin can be continued. The insulins may be premixed (usually in the ratio of 30% regular and 70% intermediate) or

TABLE III. Situations where insulin is required in type 2 diabetes

Temporary	Permanent
Severe hyperglycaemia due to an inter-current event (infection, stress); all major surgeries	When OHAs are contraindicated (e.g. chronic renal failure, chronic liver disease)
Severe hyperglycaemia at diagnosis (without significant ketones or weight loss)	OHA failure (despite using maximum effective doses)
Pregnancy	Patients with severe hyperglycaemia, weight loss, large amount of urine ketones (likely to have type 1 diabetes)

OHA oral hypoglycaemic agent

TABLE IV. Guidelines for the treatment of type 2 diabetes with insulin

Current HbA1c (%)	Present treatment	Intervention
7–10	Single OHA	Add second OHA (e.g. metformin/glitazone and sulphonylurea)
7–10	Two OHAs	Start basal insulin (preferable) or add third OHA (e.g. metformin, sulphonylurea and glitazones/ $\alpha$ -glucosidase inhibitors)
	OHA and basal insulin	Split-mix insulin (2 injections/day); stop OHA
>10	Single or 2 OHAs	Split-mix insulin (2 injections/day)
>10	Not on treatment	Initiate insulin therapy. May be able to change to OHA if the decompensating event was temporary (e.g. infection/stress) or after ‘glucotoxicity’ has decreased

OHA oral hypoglycaemic agent

TABLE V. Practical implementation of insulin regimens

Regimen	Dose distribution
Basal insulin	<ul style="list-style-type: none"> <li>Basal insulin (NPH, glargine, detemir) is given as a single dose in the evening; NPH and detemir insulin also may be given in 2 doses: morning and evening</li> <li>Initial dose is 10–12 units/day (0.1–0.2 units/kg/day); higher doses are given to obese individuals</li> <li>Monitor fasting glucose</li> <li>Insulin is increased every 1–2 weeks by 2–4 units until fasting glucose is 80–130 mg/dl</li> </ul>
Split-mix insulin	<ul style="list-style-type: none"> <li>Mixture of short- and intermediate-acting insulins or pre-mixed (30:70) insulin before breakfast and dinner</li> <li>Initial dose is 0.5–0.6 units/kg/day (higher dose in obese individuals)</li> <li>2/3rd of total dose in morning and 1/3rd in evening</li> <li>2/3rd of each dose as intermediate and 1/3rd as regular insulin</li> <li>Monitor fasting and pre-meal glucose (target 80–130 mg/dl); post-meal and 2 a.m. glucose less frequently</li> </ul>
Basal bolus regimen	<ul style="list-style-type: none"> <li>Regular (or rapid-acting) insulin before main meals and intermediate (or long-acting insulin) once or twice daily</li> <li>50% of the total daily insulin is given as intermediate or long-acting insulin; 50% in divided doses as regular/rapid-acting insulin before each meal</li> <li>Monitor fasting and pre-meal glucose; post-meal and 2 a.m. glucose less frequently</li> </ul>

NPH neutral protamine Hagedorn

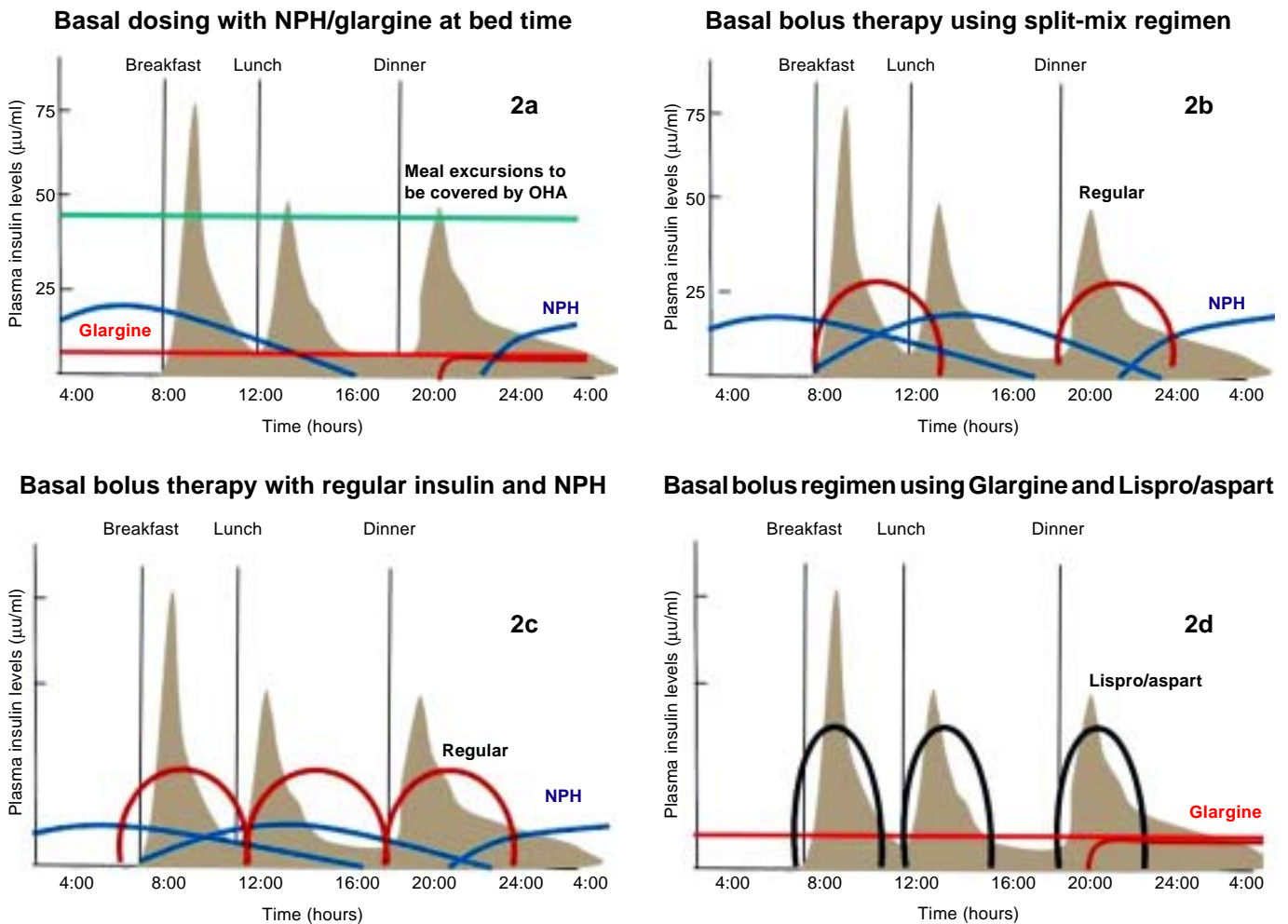


FIG 2. Schematic diagram of different insulin regimens 2a. Basal insulin therapy with NPH/glargine and oral hypoglycaemic agents (OHA) during day-time 2b. Split-mix regimen (NPH and regular insulin before breakfast and dinner) 2c. Basal bolus therapy (NPH at bedtime and before breakfast, and regular insulin before 3 major meals) 2d. Basal bolus regimen using glargine at bedtime and lispro/aspart before 3 major meals. Shaded areas represent insulin secretion in response to meals in a person without diabetes

mixed separately in a syringe. The former has the advantage of convenience while the latter has the advantage that the doses of regular and intermediate insulin can be separately adjusted according to the glucose levels.

**Basal bolus regimen.** Many patients, especially those who are obese, may not be controlled with twice daily split-mix insulin regimens. These patients will require regular insulin thrice daily (before each meal), in addition to basal insulin (twice daily intermediate or once or twice daily glargine/detemir insulin). This is the most physiological insulin regimen and also allows for the greatest flexibility.

#### Initiating insulin therapy

At the time of initiation of insulin, it is important to review the diet and, if necessary, to ask the patient to meet a dietician. The diet should be appropriate for the patient's body weight and physical activity, divided according to the insulin schedule and low in saturated fats. In addition, the patient should be strongly advised to exercise regularly, e.g. a brisk walk for 30 minutes daily.

Insulin should be initiated at a low dose and slowly titrated to higher doses (Table V). This helps to prevent hypoglycaemia. For patients starting on a single dose of basal insulin, a dose of 10–12

units at bedtime may be initiated. The dose can then be gradually increased by 2–4 units every week until fasting glucose levels come into the normal range or the patient experiences hypoglycaemia at night. For patients using a split-mix regimen, the total initial dose of insulin can be 0.5–0.6 units/kg. Here it is important to monitor both fasting and pre-meal glucose levels. The final dose is often close to 1 unit/kg or higher (in obese individuals). Whenever split-mix insulin is prescribed, the day's calories should be divided into 3 meals and 2 small snacks between meals (to prevent hypoglycaemia). Patients should be aware that the dose of insulin will change over time.

#### Day-to-day insulin adjustments

All patients on insulin should ideally monitor blood glucose at home using a glucose meter. The blood glucose should be monitored at different times each day so as to know the pattern of glucose rise and a written record should be kept in a diary. This helps in adjusting the dose of insulin. In general, the doses should be altered only after noting the glucose pattern over a few days. A summary of insulin adjustment for patients on different regimens is shown in Table VI.

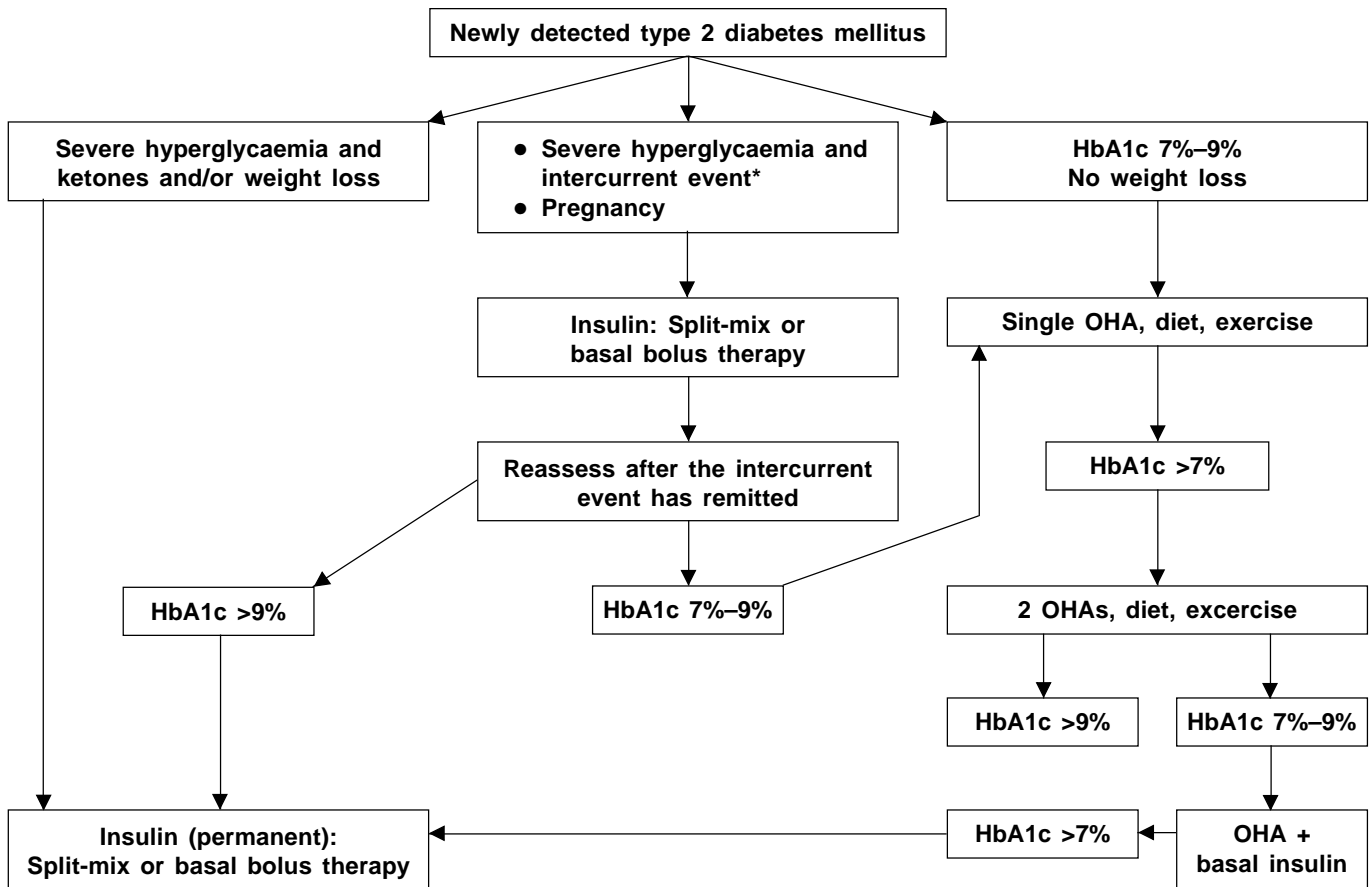


FIG 3. Flow chart for insulin use in patients with type 2 diabetes mellitus

\*Intercurrent event: Infection, major surgery and stress; severe hyperglycaemia: HbA1c >10% and fasting blood sugar >300 mg/dl; when the HbA1c levels are <7% on a particular treatment, continue the same and monitor HbA1c levels once in 6 months. OHA oral hypoglycaemic agent

CONCLUSIONS

Insulin is required at some point of time in most patients with T2DM. At the time of diagnosis of diabetes, patients and their

relatives should be informed that T2DM is a progressive disease and that insulin treatment is likely to be required at a later stage. When glycaemic control cannot be achieved on a maximum dose of OHAs, insulin should be prescribed without delay. The insulin regimen should be individualized for each patient, taking into account their age, work schedule, educational status, financial constraints as well as motivation. Different insulin regimens and a decision as to which regimen should be used is summarized in Fig. 3. Insulin therapy can be successful only if patients also follow a regular diet and exercise schedule, and regularly monitor blood glucose at home.

TABLE VI. Day-to-day insulin adjustments

Situation:	Adjustment:
Elevated/low glucose	Increase/decrease insulin
Fasting	Pre-dinner or pre-bed intermediate/long-acting
Post-breakfast	Pre-breakfast regular
Pre-lunch	Pre-breakfast intermediate-acting or pre-breakfast regular
Post-lunch	Pre-lunch regular insulin
Pre-dinner	Pre-breakfast intermediate-acting or pre-lunch regular
Post-dinner	Pre-dinner regular

Insulin doses should be increased by 2–4 units if fasting or pre-meal glucose >140 mg/dl; post-meal glucose >180 mg/dl; decisions to change insulin dose to be made on glucose levels done over 3–4 days. Insulin doses should be reduced by 2–4 units if fasting or pre-meal glucose <70 mg/dl.

SELECTED READING

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- 3 American Diabetes Association. Standards of medical care in diabetes—2007. *Diabetes Care* 2007;**30** (Suppl 1):S4–S41. [http://care.diabetesjournals.org/cgi/content/full/30/suppl\\_1/S4](http://care.diabetesjournals.org/cgi/content/full/30/suppl_1/S4)