Table II: Classification of commonly used foods based on the Glycemic index (GI)

Low GI (≤ 55)	Medium GI (56-69)	High GI (≥ 70)
Peanuts (14±8), Prunes (29±4), Soy Boiled (18±3), Rajma (19), Cherries (22), Fructose (19±2), Grapefruit (25), Barley (28±2), Whole milk (31), Low-fat milk (37±4), Skimmed milk (37±4), Yogurt (28), Red Kidney beans boiled (19), Apple (38), Green gram dal (29), Rye, Pinto beans (39), Pear (30), Plum (24), Black-eyed beans (38), Peach (34), Black beans (30), Orange (40), Boiled Carrots (33), Kiwifruit (50), Horse gram (51), Sweet Potato (41), Peas boiled (51), Buckwheat (55), Banana (51)	Apricot (57), Mango (60±16), Papaya (60±16), Whole green gram (57±6), Basmati Rice (57±4), Oatmeal (69), Ice cream (61±7), Honey (55±5), Bajra (67), Pineapple (59±8), Raisins (64±11), Cream of wheat (66), White rice (64), Beets (64±16), Boiled potatoes (58), Table sugar (63), Coca-Cola (regular) (63), Grapes (59), Brown Rice (68±4),	Watermelon (76±4), Jowar (77±8), Pumpkin (75), Ragi (84), White Baked Potato (78±4), Parsnips (97±19), Glucose (99±3), Dates (103±21), Corn flakes (81±6), White bread (75±2),

Abbreviations: GI-Glycemic Index

Carbohydrate counting

For patients using continuous subcutaneous insulin infusion (CSII), carbohydrate counting is essential. Carbohydrate counting is also beneficial for patients on a basal-bolus regimen. There are three levels of carbohydrate counting. In level 1, consistent carbohydrate intake is encouraged using an exchange or portion lists of measured quantities of food. The level 1 carbohydrate counting is useful for patients on twice daily insulin doses for whom a consistent carbohydrate intake from day-to-day is essential. Level 2 (pattern management principles) is an intermediate step. In this, patients use a consistent baseline insulin dose, continue to eat regular carbohydrates, and frequently monitor blood glucose (BG) levels to recognize patterns of BG response to carbohydrate intake and the impact of insulin doses and exercise on it. Based on this knowledge, insulin doses are adjusted for food and exercise to achieve BG goals. However, it is less commonly used primarily by the pediatric teams. Level 3 [insulin to carbohydrate ratios (ICRs)] is the most commonly recommended one and is the most appropriate for patients using multiple daily injections (MDI) or CSII. ICR varies from patient to patient based on age, sex, pubertal status, duration of diagnosis, and activity. Initially, ICR can be calculated using the formula 500 divided by total daily dose (TDD) of insulin and represents the g of carbohydrate that would be covered by 1 unit of rapid-acting insulin. Replace the number 500 with 450 for regular insulin. ICR helps to adjust the prandial insulin dose according to carbohydrate intake. Fine-tune the ratio by checking BG level before and 2 hours after the meal to maintain a BG increment of less than 60 mg/dl.

The various carbohydrate counting methods involve gram increments, 10–12 g carbohydrate portions, and 15 g carbohydrate exchanges (listed in Appendix-1). None of the methods are superior over the other. Cover all major meals and snacks containing more than 10-15 g of carbohydrates with a bolus insulin.

Dietary recommendations for specific insulin regimen

Divide daily calorie intake in 6-7 meals (3 major meals, and 3-4 snacks). In general, represent breakfast with 20% of total caloric needs, lunch, and dinner with 25- 30%, and each snack

with 10% of daily calorie inputs. Each meal should be taken at a particular time during the day with no significant and frequent deviations. A bedtime snack is considered an essential part of the regimen to prevent nocturnal hypoglycemia and should include at least 7-8 g of protein.

Most of the T1DM patients will have absolute insulin deficiency. Hence, nutritional intake should match that of a specific insulin regimen that patient is receiving. CSII and MDI provide flexibility in eating patterns, whereas pre-mix preparations and fixed insulin regimens demand food intake at fixed quantity and time. In patients on MDI with analogs or CSII, relatively higher GI major meals can be allowed, but the inter-meal snacks should contain relatively fewer carbohydrates. On the other hand, while using a basal-bolus regimen with regular insulin, relatively low GI major meals with moderate carbohydrate-containing inter-meal snacks should be encouraged.

Exercise Physiology

Exercise has multiple benefits in individuals with T1DM. Regular physical activity increases the feeling of general well-being and helps prevent obesity and mitigate increased cardiovascular risk in T1DM patients[5]. Also, although results vary across studies, regular physical activity may modestly improve glycaemic control and reduce microvascular complications[6,7]. Hence, regular physical activity should be encouraged in individuals with type 1 diabetes. Moreover, many T1DM patients may be interested in sports; instead, few may like to have sports as their careers. Hence, T1DM should not limit the ability to excel in a chosen sport.

Normal exercise physiology

The two types of exercises (aerobic and anaerobic) have diverging effects on glucose homeostasis[8]. During moderate-intensity aerobic exercise, glucose production by the liver increases 5 to 10 fold to meet the peripheral glucose supply into working muscles, in the absence of which blood glucose levels diminish below the normal range. In healthy individuals, glucose production increases up to 10-fold during maximum aerobic activity, and glucose homeostasis is maintained. During anaerobic activity, a 15-fold increase in glucose production occurs[9]. Besides, with normal islet cell function, insulin level decreases in response to diminishing BG level.

Mechanisms for exercise-associated hypoglycemia and hyperglycemia in T1DM

Exercise can cause perturbation in glucose homeostasis in T1DM individuals, hence often discouraged in them. It is difficult to predict the effect of exercise onglycemia accurately. Significant inter-individual variations are observed though intra-individual variability is less, primarily when consistency in the timing and dose of insulin, carbohydrate intake, duration, and intensity of exercise is maintained.

During aerobic exercise in T1DM, an increase in glucose disposal into skeletal muscle is often not compensated well by an increase in glucose production from the liver. Elevated insulin levels enhance the entry of glucose into muscle cells as a result of previously administered exogenous insulin (whose levels cannot be decreased unlike in those with significant endogenous insulin production) and insulin-independent mechanism (GLUT4 translocation). Moreover, elevated insulin levels effectively suppress glycogenolysis and gluconeogenesis from the liver, combating the compensatory mechanisms of hypoglycemia. Often the counter-regulatory hormone function may be compromised in T1DM individuals,

further contributing to hypoglycemia occurrence and its severity. Prior exposure to either aerobic exercise or hypoglycemia further blunts glucose counter-regulatory responses (i.e., glucagon and catecholamines).

In contrast, during anaerobic exercise, a more substantial rise in catecholamines occurs, and the pancreas in T1DM patients is not able to increase insulin secretion to offset the action of catecholamines. These factors increase glucose production by the liver while limiting glucose disposal into skeletal muscle leading to a mismatch in glucose production, utilization, and consequent hyperglycemia.

Factors affecting glucose response to exercise

Various factors such as intrinsic factors of exercise, type, and timing of insulin and food consumption, metabolic control, environmental factors affect BG response to exercise. Table III summarises these factors and their effect on the BG response.

Normal day-to-day exercise

Normal day-to-day activities are essential and part of almost every child's daily routine. Aerobic fitness may improve glycemic control. On the other hand, good glycaemic control maximizes exercise capacity.

Usually, children indulge in short periods of intense activity interspersed with periods of resting. However, occasional extra physical activity may require insulin adjustments. Once the individual gets accustomed to activities and performs them as per a predictable and regular schedule, the adjustments in diet/insulin are easier.

Hypoglycemia including late hypoglycemia and insulin adjustments

Blood glucose disposal significantly increases during aerobic exercise. Hence, when exercise is anticipated within few hours after bolus insulin (especially within one hour while on rapid-acting insulin and within three hours on regular insulin), it is advisable to reduce the pre-meal bolus dose. In children with obesity, regular administration of carbohydrates before physical activity may not help to reduce weight. Hence, especially for regular physical activities, reduced insulin dosage of previous short-acting insulin should be preferred instead of carbohydrate supplementation. However, exercise may often be spontaneous, and some patients may develop postprandial hyperglycemia with anticipatory reduction of pre-meal insulin, leading to a decrease in exercise performance. In such cases, carbohydrate consumption before an activity is the preferred strategy to maintain blood glucose levels. In patients using CSII, setting a temporary lower basal rate (50% to 80% reduction in basal dose depending upon the duration and intensity of the exercise, which should be done at least 90 min before the initiation of activity and lasting till the activity stops) may be considered.

Insulin sensitivity increases during and immediately after the exercise and again 7-11 hours after the completion of the exercise. Glucose requirement increases during these periods of heightened insulin sensitivity and increases the risk of hypoglycemia for 24 hours after the exercise. Hence, reducing the basal insulin by 10-20% or extra-low GI snacks at bedtime should be considered on the day of exercise. Consider a 30-50% reduction in the basal insulin of the previous day and on the day of activity for all-day or prolonged activities. The use of continuous glucose monitoring (CGM) during exercise in patients who are on CSII with low glucose suspension facility is beneficial in preventing hypoglycemia. Even

Table III: Factors affecting and their effect on the BG response to exercise

Factor	Effect on glycemia
Duration of exercise	Nearly all forms of activity lasting >30 min require some adjustment to food or a reduction in insulin.
Intensity of exercise	Increase in the intensity of exercise increases the risk of hypoglycemia requiring more significant insulin decrements.
Type of exercise	Anaerobic efforts increase the BG level due to the release of epinephrine and glucagon. On the other hand, aerobic activities can lower BG levels during (usually within 20–60 min after the onset) and after the exercise. Combining intermittent bouts of anaerobic exercise with aerobic forms may prevent hypoglycemia during long-duration aerobic activities. Weight-bearing activities may cause hyperglycemia due to the release of growth hormones, and the performance of these activities before aerobic activities may prevent hypoglycemia.
Timing of exercise	Morning activity, done before insulin administration, is less likely to result in hypoglycemia as circulating insulin levels are typically low, and glucose counter-regulatory hormones may be high.
Conditioning	Hypoglycemia is less with regular conditioning. It may be due to the reduction of insulin in anticipation or the better utilization of lipids as fuel.
Degree of stress/ competition in the activity	Like high-intensity activity, stress may also increase catecholamine release and elevate BG levels, requiring corrective insulin administration.
Muscle mass/ number of muscles used in the activity	Exercises that involve a higher number of muscles during aerobic exercise lead to a higher drop in BG. More significant energy consumption occurs during weight-bearing activities than non- weight-bearing activities.
The long term metabolic control	Suboptimal control may reduce aerobic capacity and may cause easy fatigability.
Hyperglycaemia during exercise	May reduce exercise tolerance.
Type and timing of insulin	Rapid-acting insulins typically cause hypoglycemia 60-90 min after administration, whereas regular insulin does so at 2-3 hours.
Choice of injection site	Injection of insulin in the exercising muscle leads to the rapid absorption of insulin.
Ambient temperature	Insulin absorption is increased by high temperature and decreased by low temperature.

Abbreviations: BG: Blood Glucose

otherwise, the use of CGM and appropriate management of down trending BG levels can reduce hypoglycemia. Suggest monitoring BG levels at regular intervals in patients not using CGMS and performing unaccustomed activities and act accordingly. Supplement carbohydrates adequately in patients in whom regular BG monitoring cannot be done, and any person who develops clinical features of hypoglycemia should receive glucose tablets or other forms of quick-acting carbohydrates.

Ketones

Significant hyperglycemia (random BG level > 250 mg/dl) with any degree of ketonuria indicates under insulinisation. These patients are likely to experience a further rise in blood glucose with exercise due to the unopposed action of counter-regulatory hormones and impaired glucose uptake by the muscles. The latter also compromises the exercise performance. Ketone production may also increase rapidly and may precipitate ketoacidosis, which may manifest with pain in abdomen and vomiting. Hence, do not recommend exercise in all individuals with type 1 diabetes who have hyperglycemia with any degree of ketonuria (small or more) or ketosis (blood β-hydroxybutyrate is > 0.5 mmol/L).

Parents often believe that prolong exercise does not require insulin. Unless long-acting insulin provides cover, monitor blood glucose levels carefully during exercise, because skipping the previous dose of short-acting insulin could be dangerous. If the previous insulin dose is skipped, the child's monitoring should include ketone testing, preferably blood ketone levels using glucometer devices, equipped to measure blood ketones. The latter provides an excellent method for rapid detection and exact measurement of ketones. Blood ketone measurement is also a better marker of resolution of ketosis than urine ketones.

On the other hand, few patients are afraid that reducing the pre-exercise insulin doses may lead to ketosis during or after exercise; however, reducing insulin down to 25% of pre-exercise doses does not increase the risk of ketosis.

Nutritional management of exercise and physical activity

Individuals with T1DM should receive some carbohydrate snacks before physical activity. If pre-exercise insulin doses are appropriately reduced, a carbohydrate intake of 0.3-0.5 g/kg/h of moderate physical activity may be sufficient. A relatively lower BG level at the initiation of physical activity and not adjusting the insulin doses before physical activity increases the hypoglycemia risk despite being in the fed state. The occurrence of hypoglycemia on the previous day blunts the autonomic and counter-regulatory response to hypoglycemia. Hence, in all these situations, 2-3 times more carbohydrates (1.0-1.5 g/kg/h) need to be supplied to prevent hypoglycemia. Table IV summarises the suggestions for carbohydrate intake during physical activity.

For activities lasting more than 30-60 min, prefer slow-releasing carbohydrates, whereas for activities lasting less than 30-60 min moderately fast releasing carbohydrates should be administered. Prefer administration of foods containing fat or protein with carbohydrates (e.g., chocolates, milk, curd, etc.) for the former situation and prefer predominant carbohydrate foods (e.g., fruits, a cereal) for the latter. It is essential to maintain adequate hydration before, during, and after the exercise to achieve optimal exercise performance.

Exercise recommendations for individuals with T1DM

For adults with T1DM, recommend 150 min or more of moderate-to-vigorous intensity activity per week spread over at least three days/week but without more than two consecutive days of no activity. Adults with T1DM should also engage in 2-3 sessions per week of resistance exercise on non-consecutive days.

Table IV: Suggestions for carbohydrate intake during physical activity

< 90 mg/dl	Ingest 0.3-0.5 g/kg/h of quick-acting carbohydrate and increase BG level to ≥ 90 mg/dl before initiating exercise. For prolonged activities, consume additional carbohydrate (0.5–1.0 g/kg/h of exercise) based on BG testing results.
90–150 mg/dl	Consume carbohydrates (0.8–1.0 g/kg/h) starting from the onset of exercise.
150–250 mg/dl	Start an exercise and avoid consumption of carbohydrates until BG levels are < 150 mg/dl.
> 250 mg/dl	Check for ketones and avoid exercise if ketones are moderate-to-large. If BG 250-350 mg/dl and ketones are negative, initiate mild-to-moderate intensity exercise but delay intense exercise until BG level is < 250 mg/dl. If ketones are negative but BG > 350 mg/dl consider insulin correction by ~ 50% depending on the active insulin.

Abbreviations: BG- Blood Glucose

For children and adolescents with T1DM, recommend 60 min/day or more of moderate or vigorous-intensity aerobic activity. Besides, recommend vigorous, muscle-strengthening, and bone-strengthening activities at least three days a week.

Precautions for exercise

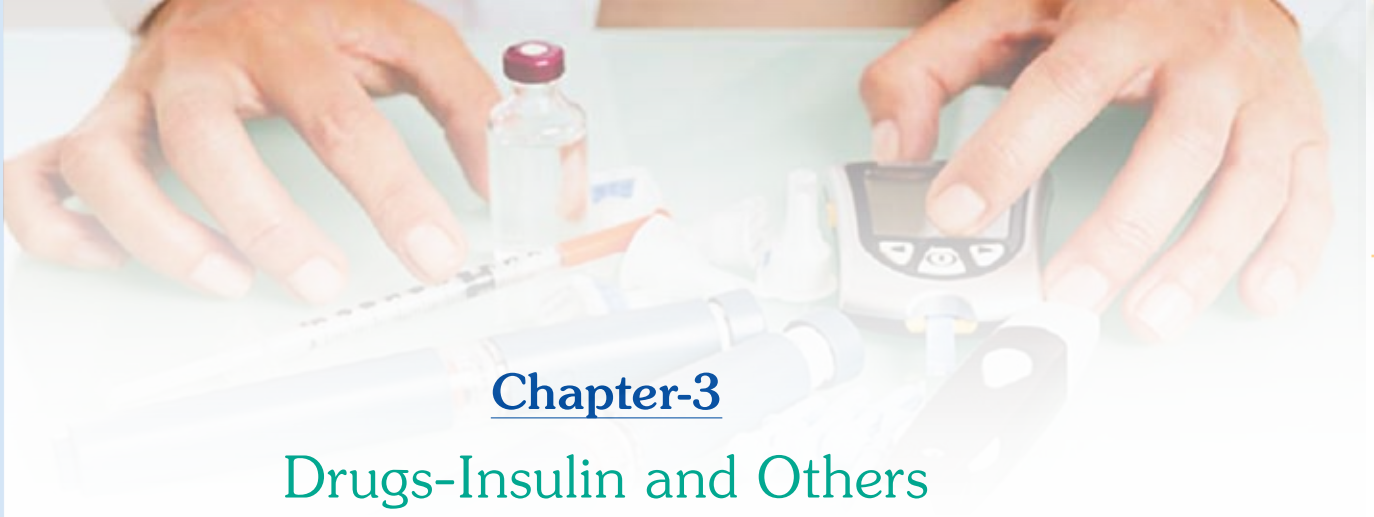
T1DM individuals with signs and symptoms of cardiovascular disease (CVD), any diabetes-related complications (microvascular or macrovascular), or previously sedentary patients older than 30 years of age (and those who have had diabetes for ten years or longer) should undergo evaluation for CVD before starting new exercise programs. Vigorous exercise is contraindicated in patients with severe NPDR or PDR to reduce the risk of vitreous hemorrhage.

References

1. de Bock M, Lobley K, Anderson D, Davis E, Donaghue K, Pappas M, et al. Endocrine and metabolic consequences due to restrictive carbohydrate diets in children with type 1 diabetes: An illustrative case series. *Pediatr Diabetes.* 2017 Apr 11. doi: 10.1111/pedi.12527. [Epub ahead of print]
2. Roskjær AB, Andersen JR, Ronneby H, Damm P, Mathiesen ER. Dietary advices on carbohydrate intake for pregnant women with type 1 diabetes. *J Matern Fetal Neonatal Med.* 2015 Jan;28(2):229-33.
3. Joshi SR, Bhansali A, Bajaj S, Banzal SS, Dharmalingam M, Gupta S, et al. Results from a dietary survey in an Indian T2DM population: a STARCH study. *BMJ Open.* 2014 Oct 31;4(10):e005138.
4. Fitch C, Keim KS; Academy of Nutrition and Dietetics. Position of the Academy of Nutrition and Dietetics: use of nutritive and non-nutritive sweeteners. *J Acad Nutr Diet.* 2012 May;112(5):739-58.
5. Herbst A, Kordonouri O, Schwab KO, Schmidt F, Holl RW; DPV Initiative of the German Working Group for Pediatric Diabetology Germany. Impact of physical activity on cardiovascular risk factors in children with type 1 diabetes: a multicenter study of 23,251 patients. *Diabetes Care* 2007; 30(8): 2098–100.
6. Quirk H, Blake H, Tennyson R, Randell TL, Glazebrook C. Physical activity interventions in children

and young people with type 1 diabetes mellitus: a systematic review with meta-analysis. *Diabet Med* 2014; 31(10): 1163–73.

7. Kriska AM, LaPorte RE, Patrick SL, Kuller LH, Orchard TJ. The association of physical activity and diabetic complications in individuals with insulin- dependent diabetes mellitus: the Epidemiology of Diabetes Complications Study–VII. *J Clin Epidemiol* 1991; 44(11): 1207–14.
8. Riddell MC, Perkins BA. Type 1 diabetes and exercise. Part I: applications of exercise physiology to patient management during vigorous activity. *Can J Diab* 2006;30(1):63–71.
9. Raguso CA, Coggan AR, Gastaldelli A, Sidossis LS, Bastyr EJ III, Wolfe RR. Lipid and carbohydrate metabolism in IDDM during moderate and intense exercise. *Diabetes* 1995;44(9):1066---1074.
10. Smart CE, Annan F, Bruno LP, Higgins LA, Acerini CL. International Society for Pediatric and Adolescent Diabetes. ISPAD Clinical Practice Consensus Guidelines 2014. Nutritional management in children and adolescents with diabetes. *Pediatr Diabetes* 2014 Sep;15 Suppl 20:135-53.



Chapter-3

Drugs-Insulin and Others

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Introduction

All children and adults with type 1 diabetes (T1DM) require insulin as soon as they are diagnosed and continuously thereafter throughout life. Short-acting bovine insulin was first used in the treatment of a 14-year-old child with T1DM in 1922. Since then, there have been many improvements in available insulin formulations, and also in the regimens of insulin therapy. These include the availability of recombinant human insulin since 1982 and bio-engineered insulin with rapid-action (insulin lispro, insulin aspart, and insulin glulisine), ultra-rapid action (fast-acting insulin aspart) as well as specially designed insulins with longer duration and relatively "peakless" action (insulin glargine U-100, insulin glargine U-300, and insulin degludec). In addition, the previous regimens using twice daily "split-mix" insulin regimens have been mostly superseded by more physiological "intensive" regimens with multiple daily insulin injections (MDII) or continuous subcutaneous insulin infusion (CSII). It has been clearly shown in the Diabetes Control and Complications Trial (DCCT) study that intensive glycemic control, using either MDII or CSII, improves hemoglobin A1c (HbA1c) and reduces progression of diabetic microvascular complications in patients with T1DM[1].

Whatever the insulin regimen, their optimal use depends on the painstaking care taken by a diabetes team, including the physician, diabetes educator and nutritionist to educate and support the patient and his/her family regarding their best use as well as insulin dose adjustment. In addition, while it is essential to strive for the best HbA1c feasible (< 7.5% in children and < 7% in adults), the type of insulin used and insulin regimen will differ from patient to patient. Factors such as motivation, education, and financial resources of the family should be considered while making this decision. The co-operation of the patient, and support of the family members, are key to achieving good glycemic control in T1DM.

Types of insulin

The different types of insulin available and their action profile have been shown in Table I[2-4].

Short-acting recombinant regular human insulin (plain, soluble) is the most commonly used bolus (or prandial) insulin to prevent post-meal glucose elevation. The earlier used insulin formulations which were derived from other sources (such as porcine and bovine insulin) are no longer available in India.

Conventional insulin formulations

Regular insulin is used along with intermediate actingor long-actinginsulin in "split-mix", "pre-mix" and "basal bolus" regimens. Regular insulin should be administered 20-30

Table I: Action profiles of different insulin preparations on subcutaneous administration

Type of insulin	Onset of action	Peak action (h)	Duration (h)
Regular	30-60 min	2-4	6-8
Rapid-acting analog (aspart, lispro, glulisine)	5- 15 min	1-2	3-5
Ultra-rapid acting analog (fast-acting insulin aspart)	3-5 min	1	3-4
NPH	1-3 h	5-7	12-16
Detemir	2-3 h	6-8	12-24
Glargine U-100	2-3 h	Peakless	20-24
Glargine U-300	4-6 h	Peakless	>24 (about 36 h)
Degludec	1-4 h	Peak less	>24 (about 42 h)

Abbreviation: NPH: Neutral Protamine Hagedorn

minutes before meals for optimum effect; its effect peaks at 3-4 hours and total duration of action is approximately 6-8 hours. It can be used via the intravenous route in diabetic ketoacidosis, during perioperative period or labor.

Intermediate-acting insulin (NPH) is used as a basal insulin in split-mix or pre- mix (twice daily insulin) regimens and in basal-bolus regimens. This preparation cannot be given by intravenous route or in insulin pumps. In contrast to newer basal insulin formulations, NPH insulin does not have a uniform action and has a pronounced peak after 6-8 hours and the effect tails off in 12-14 hours.

Insulin analogs

Rapid-acting insulin analogs have quicker onset and shorter duration of action as compared with regular insulin (Table I). The currently available preparations include aspart, lispro and glulisine insulin. They have essentially similar properties, and are given 5-10 minutes before food because of their quicker action as compared with regular insulin. Also, they have an earlier and higher peak compared with regular insulin and thus are useful in diminishing immediate post-prandial hyperglycemia. Their shorter duration of action decreases the risk of subsequent delayed hypoglycemia. Recently introduced ultra-rapid acting insulin analog, that is, “fast acting insulin aspart” (Fiasp, Novo Nordisk) has an onset of action at 3-5 minutes and duration of action of 3-4 hours, compared to 10-15 minutes and 3-5 hours, respectively with rapid acting analogs. Ultra-rapid acting insulin analog (administered immediately before meal or up to 20 minutes after meal) and rapid acting insulin analogs (may be administered immediately before meal in selected cases) offer special advantages in toddlers with T1DM who are moody and refuse to eat or throw up after a meal, compared to regular insulin (which carries an increased risk of hypoglycemia in such a scenario). Besides, these formulations are also helpful in school or college going children and teenagers, and office going adults with T1DM who have limited recess time and therefore, observing a gap of 30 minutes before a meal is not feasible. A latest development in this field is “ultra-rapid acting insulin lispro” (Lyumjev, Elli Lilly) which has been approved for use in adults with T1DM and T2DM by the US FDA.

Basal insulin analogs include insulin glargine (U-100 and U-300), insulin detemir and recently introduced insulin degludec. These preparations (especially, insulin glargine and

insulin degludec) are relatively "peakless" and have a sustained action over 24 hours (except for detemir which has a slightly shorter action of 12-24 hours). Most studies show a reduced risk of nocturnal hypoglycemia with basal insulin analogs compared to NPH, though there is only a modest improvement in HbA1c levels in patients with T1DM[5]. Detemir is often used as twice daily injection, while glargine and degludec are frequently utilized as a single daily injection.

Insulin mixing

Regular and NPH insulin can be mixed together for use in a syringe (split-mix regimen). For this purpose, regular insulin should be drawn in syringe first, followed by NPH insulin (see Box 1).

Box 1: Preparing an injection of regular and NPH insulin using insulin vial for split-mix regimen

1. Allow insulin vials to reach room temperature and check that there are no clumps or particles.
2. Turn the NPH bottle on its side and gently roll it between the palms. Do not shake vigorously.
3. Clean the top of the vial with an alcohol swab.
4. Take the NPH insulin vial and inject an amount of air equal to the dose of NPH insulin required. Do not draw insulin. Remove the needle from the vial.
5. Take the vial with regular insulin, clean top with alcohol, and inject air of an amount equal to the regular insulin dose.
6. With the needle still in the vial, turn the vial upside down and pull the plunger to fill the syringe with the desired dose. Remove any air bubbles from the vial.
7. Re-insert the needle into the vial of NPH insulin, slowly draw the correct amount of insulin and remove the needle from the vial.
8. The syringe is ready for injecting.

Abbreviation: NPH: Neutral Protamine Hagedorn

Similarly, rapid acting analogs can be mixed with protaminated regular insulin (NPH) or protaminated analog insulin. Insulin glargine cannot be mixed with any other insulin due to its acidic pH. Pre-mixed formulations of regular insulin and NPH (such as Huminsulin 30/70, Mixtard 30/70, Mixtard 50/50), rapid acting insulin analog and protaminated analog insulin (such as Novomix 30/70, Humalog Mix 25/75, Eglucent Mix 25/75), and insulin aspart and insulin degludec (Ryzodeg 30/70) are readily available in the market.

Insulin strengths

In India, human regular and NPH insulin are available in strengths of 40 units/ml and 100 units/ml in vials. All insulin (regular, NPH, analogs) in pen cartridges have a strength of 100 units/ml.

Insulin color coding

There is a universal color coding for each insulin preparation which has been standardized worldwide. This means that a given preparations of insulin should have a fixed color on the label, regardless of the manufacturer. The color coding for various preparations of insulin has been described in Table II.

Table II: Color coding of different insulin preparations

Insulin preparation	Color code
Rapid-acting insulin analog Aspart Lispro Glulisine	 Orange Dark brown Dark purple
Short acting insulin Regular	Yellow
Intermediate acting insulin NPH	Green
Basal insulin analog Glargine Detemir	 Purple Dark green
Premix Insulin conventional 30/70 50/50 25/75	 Brown Grey Sky blue
Premix insulin analog Aspart plus protaminated aspart (30/70) Lispro plus protaminated lispro (25/75) Lispro plus protaminated lispro (50/50)	 Deep blue Golden yellow Red

Abbreviation: NPH: Neutral Protamine Hagedorn

Storage and stability of insulin

At the time of purchasing the insulin, the expiry date should be checked and it should be ensured that there are no clumps or discoloration of the insulin. Extra vials or cartridges of both short/rapid-acting as well as intermediate/long-acting insulin should always be available at home.

At room temperature (25^{0}C), insulin will lose < 1% of its potency over a month, while at higher temperatures there will be a greater loss of potency[6]. Exposure to direct sunlight or heat damages insulin and it will lose its potency. Insulin should never be frozen. The unopened insulin vial or cartridge should be kept in the refrigerator shelf for long-term use, where it will retain its potency till the expiry date. Once opened, the insulin vial can be kept at room temperature for up to 1 month in cooler climates or during winter months. In all other circumstances, it would be best to store the opened insulin vial in a refrigerator where it will be stable for 1 month. In hot climates, when a refrigerator is not available, the vials can be kept in an earthenware pot with wet sand or cooled thermos flasks. While travelling, it is convenient to use ready-made "cool packs" which are previously frozen in the ice compartment of the refrigerator. Alternatively, the vials should be kept in plastic wrapper and placed in a cold thermos. During travel, insulin (and other supplies) should always be stored in the personal luggage. During a flight, insulin should not be placed in the check-in luggage since it may be exposed to extremes of temperature (see chapter on "Special group-Pregnancy, Travel and Surgery"). It should be always be checked that the electrical supply is adequate and insulin is appropriately stored at the medical shop from where insulin is procured.

Unopened insulin cartridges/disposable pens can be stored in the refrigerator until their expiry date. Once in use, they can be stored at room temperature (below 25-30^{0}C) for 1 month. In warmer climates, they can be stored in the refrigerator (without needles attached)

for up to 1 month. Insulin pens should never be stored with the needles attached since air may be drawn in.

Insulin needles

The thickness of skin (epidermis plus dermis) has not been found to vary significantly with age, body mass index, ethnicity and gender in adults with diabetes. The mean skin thickness by ultrasound measurements is about 2.2 mm. However, since subcutaneous tissue thickness varies with body mass index, lean individuals are at increased risk of intramuscular injections with longer needles. The needle length should therefore be selected accordingly and in selected individuals, the risk of intramuscular injection may be further minimized by: a) lifting a fold of skin before injecting, and b) injecting at an angle of 45-60^{0}C instead of 90^{0}C. The length of needles recommended for injecting insulin in most children and adults is 4-6 mm. For extremely lean individuals, a skin fold should be raised even with 4 or 5 mm needles. The needles for insulin syringes are available in lengths of 6,8 and 12.7 mm (29-31 G) while pen needles are available in lengths of 4,5,6 and 8 mm (30-32 G)[7].

Injection sites

In most clinical circumstances, insulin is injected subcutaneously. Care should be taken to avoid an intradermal injection, since it is painful and insulin is not well absorbed. In addition, intramuscular injections should be avoided since absorption occurs more rapidly compared to a subcutaneous injection, increasing the risk of hypoglycemia. Preferred sites for injection are abdomen (at least four finger breadths away from umbilicus), anterolateral aspect of thigh, deltoid region and upper-outer quadrant of buttock. Injecting on deltoid region and buttocks require the help of another person, while the patient alone may inject on abdomen and thigh. The forearm and calves should never be used for insulin injections. In general, the same region should be used for injection at different times of the day, but the exact sites should be changed daily (e.g. moving 0.5-1.0 inch from a previous site in a clockwise or anticlockwise manner on one quadrant of the abdomen or one half of the thigh). In young children, the deltoid region and buttocks should be avoided. This is because of the small muscle mass in the arms and proximity to sciatic nerve in the gluteal region. Injections in abdomen result in faster absorption and are less affected by exercise. Hence, the site is suitable for injecting faster-acting insulin preparations. Absorption from the thigh is slower, but can increase if the legs are involved in exercise. Hence, injection at this site should be avoided when it is likely that the running or similar vigorous exercise will be performed, since this may lead to hypoglycemia.

Injection site pain

Pain from insulin injection can be reduced by using smaller and narrow gauge needles, changing needles after a single use (where possible), avoiding injection of cold insulin (taking insulin out of refrigerator about 30 minutes before injecting) and using insulin injection aids and distraction techniques. Insulin needles are coated with silicone to make the injection virtually painless; use of an alcohol swab for cleaning the site and injecting before the area is dry may lead to loss of needle's silicone coating and make the injection painful. The site chosen for insulin injection should be clean and dry; if visibly dirty, it can be cleaned with soap and water, however, use of alcohol swab to clean the site is not recommended. Besides, while changing needle after a single use is helpful to reduce

the pain associated with the repeated use of a blunt needle, it may not be cost-effective, especially in a resource constrained setting like ours. Therefore the cost-effective practice of "multiple use of needles till the tips feel blunt" may be employed.

Side effects of insulin therapy

1. ***Hypoglycemia:*** Hypoglycemia is the most frequent side effect of insulin treatment and is a major deterrent in achieving tight glycemic control. While prescribing insulin, patient should be clearly explained about the symptoms of hypoglycemia, its management and possible factors (such as exercise, delayed or skipped meals) which can cause hypoglycemia.
2. ***Weight gain:*** Weight gain may occur due to improved glycemic control, recurrent hypoglycemia leading to increased hunger, and direct lipogenic effects of insulin on adipose tissue.
3. ***Lipohypertrophy and lipoatrophy:*** Lipohypertrophy occurs due to injection of insulin at the same site and repeated use of a blunt needle. Since the lipohypertrophic site is relatively painless, patient prefers to inject insulin at the same site, leading to further hypertrophy and variable insulin absorption. Injection sites should be examined periodically by both physician and patient, especially in setting of unexplained blood glucose variability. Rotation of sites should be strictly adhered to and needle changed periodically (ideally after each injection) to prevent this condition. Lipoatrophy, defined as localized loss of fat is a rare phenomenon in the current day due to introduction of purified insulin preparations.
4. ***Insulin site infection*** (see chapter on "Acute complications-Diabetic Ketoacidosis, Hypogycemia and Infections").

Insulin delivery devices

Insulin syringes: In India, insulin syringes with two different markings viz. 40 IU/ ml (U-40) and 100 IU/ml (U-100) are available. U-40 syringe has a red cap and markings upto 40 at interval of one unit, while U-100 syringe has an orange cap with markings upto 100 at interval of two units (each division of U-40 and U-100 syringe equals one unit and two units of insulin respectively). It is important to ensure that the patient uses the correct insulin syringe- 40IU/ml for U40 insulin vial and 100IU/ml for U100 insulin vial.

Disposable plastic insulin syringes are designed for single use. Reuse should be avoided as far as possible since it may result in infections. If this is not feasible due to high cost, the syringes should be changed daily. Used needles and syringes should always be cut and then discarded into a tin or plastic container which cannot be tampered with.

Injection aids include subcutaneous indwelling catheters which are useful to overcome multiple pricks and resulting pain. Automatic injection devices and jet injectors are other options for insulin injection in children. These are only required in special cases where the child or adult is very apprehensive of conventional injections.

Pen devices: Pen devices contain insulin in pre-filled cartridges. Pens may be re-usable with separate insulin cartridges, or may be available as pre-filled disposable pens. Half unit pens are available and are useful for giving small doses in young children. With a pen device, there is no need to draw up insulin; hence chances of inadvertently taking a

wrong dose are minimized. Also, the risk of contamination of insulin is reduced. It is far more convenient to carry the pen device to school, work place or travel compared with syringes and insulin vials. The main disadvantage is higher costs compared to insulin vials. In addition, administering regular and NPH insulin in a single injection (in the context of split- mix regimen) is not possible with a pen device.

Insulin infusion device: An insulin infusion pump essentially consists of an insulin reservoir and a pump[8]. The insulin reservoir is connected to a cannula with a needle which is inserted subcutaneously at one site in abdomen for 2-3 days. Most insulin infusion pumps use rapid acting insulin analogs (aspart, lispro and glulisine) for continuous insulin delivery by subcutaneous route. The rate of insulin infusion is programmable by the patient, using the in-built software. The patient (in discussion with treating physician) can set and adjust insulin infusion rate for basal coverage which can be further divided into multiple segments and administer bolus doses of rapid acting insulin via the pump device immediately before a meal (or snack). The device can be worn by the patient e.g. on a belt. The newer insulin pump devices are able to communicate with a continuous glucose monitor system (CGMS) and utilize CGMS glucose values to temporarily suspend insulin delivery before an episode of hypoglycemia (threshold suspend insulin pump, Medtronic MiniMed 530 G) and adjust basal insulin infusion rates via an in-built algorithm (hybrid closed loop insulin pump, Medtronic MiniMed 670G).

Insulin injection technique

Insulin taken out from the refrigerator should be allowed to come to room temperature before injecting (approximately 30 minutes). Before injection, it has to be ensured that no air bubbles are sticking in the needle. Insulin should never be given through clothing, a practice not uncommon among young adolescents. Cleaning of the skin with an alcohol swab is not essential since most insulin preparations contains anti-bacterial agents which inhibit growth of bacteria commonly found on skin and the use of alcohol may lead to loss of silicone coating of insulin needles (see above). However, if the site is visibly dirty, it should be cleaned with soap and water and allowed to dry before injecting. Insulin injection devices should never be shared. The details of the drawing insulin and the injection technique are provided in boxes 1-3.

Box 2: Preparing an insulin pen for injection

1. Attach a fresh pen needle to the pen. Remove the cap from the needle.
2. In case of pen with NPH insulin, slowly mix the insulin by inverting 5 times.
3. Remove 2 units of insulin and inject into the air to prime the pen.
4. Turn the dial on the pen to the prescribed dose.

Abbreviation: NPH: Neutral Protamine Hagedorn

Insulin dose

An optimal insulin dose is one which will achieve good glycemic control without frequent hypoglycemic episodes. With an appropriate dose, a child should be able to have appropriate growth and development. During the initial presentation, total daily insulin dose may be high due to increased counterregulatory hormones and the suppression of insulin secretion due to glucotoxicity. A few weeks or months after diagnosis, the dose may decrease ("honey moon phase"), with a requirement < 0.5 IU/kg/day. This phase lasts for

Box 3: Insulin injection technique

1. Select an appropriate injection site (always rotate sites).
2. Make sure that the skin is clean. In case, the site is visibly dirty, clean with soap and water and allowed the area to dry before injecting.
3. Pinch 1-2-inch portion of skin and fat between the thumb and first finger.
4. With the other hand, hold the syringe or pen like a pencil, insert into the skin at a 45^0 angle (children and adolescents) or perpendicularly (most adults), and inject with one motion.
5. Push the plunger steadily with the thumb until the insulin is fully injected. Keep the needle in the skin for 10-15 seconds.
6. Remove the needle. If needed, press the injection site for 5-10 seconds to prevent the insulin from leaking out.
7. Remove the needle from the syringe/pen and dispose in tin or plastic box.

some weeks or months, after which requirement increases and a pre-pubertal child requires nearly 0.7-0.9 IU/ kg/day. During puberty, the requirement often increases (1.2-2 IU/kg/ day), due to increasing insulin resistance resulting from higher levels of growth hormone and sex hormones and gradually reduces after puberty. In addition, insulin requirement differs in each individual and varies at different times of the day and in relation to meals and exercise.

Other major factors which can affect insulin requirements are body weight, stress, underlying infections, renal impairment and adrenal insufficiency and concomitant autoimmune disorders, hypothyroidism and celiac disease.

Insulin regimens

The aim is to mimic as closely as feasible the physiological action of insulin in relation to the time of the day, including meals, snacks and exercise, and to avoid hypoglycemia. This can be achieved by different insulin regimens:

1. Split-mix regimen

In this regimen, both short acting (regular) insulin and intermediate acting (NPH) insulin are given in the morning before breakfast and before dinner. Approximately half of the total daily dose (TDD) is given as basal insulin and remaining as prandial insulin. Patients on this regimen require approximately 2/3rd of TDD in the morning and the remainder at night. This regimen has the advantage of reducing insulin injection pricks to 2 times/day. However, the morning NPH insulin peak is often inadequate to cover lunch and tea time snacks, while there is frequent pre-lunch hypoglycemia (due to combined effect of both regular and NPH insulin). In addition, the scope for adjustment of insulin is limited and it is essential that snacks and meals, specially lunch, do not vary in time or quantity. Hence, this regimen is not ideal for most children and adults with T1DM.

2. Pre-mix regimen

Pre-mixed insulin preparations containing short acting insulin (or rapid-acting insulin analog) and NPH insulin (or protaminated insulin analog) in a fixed ratio (30:70; 25:75; 50:50) are ready to use, commonly available, cheap and effective. However, because of a fixed ratio, the dose of short and intermediate acting insulin cannot be adjusted