Bangladesh Endocrine Society (BES)
Insulin Guideline

First Edition 2018
Reprint 2019

Published by
Bangladesh Endocrine Society (BES)
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First Edition 2018
Published
02 November 2018, Dhaka, Bangladesh
Reprint 2019

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Printing: By Design

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Preface

Inception of creation of "Bangladesh Endocrine Society (BES) Insulin Guideline" was made by Executive Committee (2016-2018) of Bangladesh Endocrine Society (BES), on its 2nd EC Meeting held on 03 March 2017, through a newly formed Scientific Sub-committee.

Subsequently, the Scientific Sub-committee of BES appointed BES Insulin Guideline Task Force to make the dream come true. The endeavor became evident on 13th BES EC meeting, held on 18th August 2018, where the first edition of "Bangladesh Endocrine Society (BES) Insulin Guideline" was submitted to EC. Approval of first edition was done after reviewing of suggestions of all the members of Executive Committee.

The purpose of creating this manual is to serve clinicians regarding insulin uses in different clinical scenarios considering resource availability and circumstances prevailing in Bangladesh.

Heartfelt gratitude goes to all members of the BES Insulin Guideline Task Force who have worked for more than a year-long to bring the vision into daylight. We express thanks to the Scientific Sub-committee of BES [2016-2018] for their efforts and guidance all through its journey.

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Abbreviations

BES	Bangladesh Endocrine Society
CV	Cardiovascular
CGM	Continuous Glucose Monitoring
CSII	Continuous Subcutaneous Insulin Infusion
DPP4i	Dipeptidyl Peptidase - 4 Inhibitor
DM	Diabetes Mellitus
DKA	Diabetic Ketoacidosis
eGFR	Estimated Glomerular Filtration Rate
FPG	Fasting Plasma Glucose
GDM	Gestational Diabetes Mellitus
HHS	Hyperosmolar Hyperglycemic State
MNT	Medical Nutrition Therapy
MDI	Multiple Dose Insulin
OAD	Oral Antidiabetic Drugs
PPG	Post Prandial Plasma Glucose
SMBG	Self Monitoring of Blood Glucose
SGLT2i	Sodium Glucose Co-transporter 2 Inhibitor
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
U	Units
Kbw	Kg Body Weight
αGi	Alpha Glucosidase Inhibitor

Section 1: Insulin is a life-saving hormone.

Introduction

Key Points:

- *Insulin still remains the oldest and arguably the best treatment option for diabetes.*
- *Early initiation of insulin in the course of diabetes has many beneficial effects.*
- *Discovery of insulin in 1921 by Banting, Best, James Collip and Macleod changed the horizon of diabetes management.*
- *Currently available insulin preparations can be divided into two types- conventional insulins and insulin analogues.*
- *There are some distinct advantages of insulin analogues over the conventional insulins: mealtime flexibility, less absorption variability, peak-less profile of basal insulin, and less chance of early post-meal hyper and late post meal hypoglycemia by the rapid acting bolus insulins.*

Diabetes mellitus is a metabolic disorder characterized by chronic or persistent hyperglycemia, due to defect in insulin secretion and/or insulin action. In the pre-insulin era it was a rapidly fatal polyuric disorder; the discovery of insulin has transformed its natural history into a chronic and complex condition resulting in significant morbidity and mortality. In 2015 the estimated number of people with diabetes worldwide was 415 million, which is projected to become 642 million by the year 2040. About 5 million adults died from diabetes in 2015[1]. In Bangladesh, the overall age adjusted prevalence of diabetes was 7.4% in 2015[2].

Life style modification (including medical nutrition therapy and physical exercise) and pharmacologic agents remain the cornerstone of management of diabetes. Currently we have a good number of oral antidiabetic agents, starting with the sulfonylureas and biguanides since 1950s, followed by the alpha glucosidase inhibitors, thiazolidendiones, DPP-IV inhibitors and the most recently added SGLT-2 inhibitors. GLP-1 agonists and amylin analogues are also available as non-insulin injectable antidiabetic agents. However, insulin still remains the oldest and arguably the best treatment option for diabetes.

Many studies suggest that insulin initiation early in the course of diabetes has many beneficial effects, including preservation of β-cell function. It has been found that people who experienced the greatest improvements in β-cell function were able to maintain normoglycemia for longer period with lifestyle management alone. Early intensive insulin therapy was observed to increase serum adiponectin and nitric oxide concentrations, decreased TNF-α levels and significantly improved endothelial injury/dysfunction, thereby exerting beneficial effects on the vasculature. Meta-analyses of several prospective studies investigating the effect of intensive glycemic control on CV outcomes suggest that intensive glycemic control reduces the risk of CV outcomes without increasing the risk of mortality. Therefore, it is beneficial for people with type 2 diabetes having high HbA1c levels to start insulin early for normalization of their glycemic status, after which they can be moved onto standard care[3].

Discovery of insulin in 1921 by Banting, Best, Collip and Macleod changed the horizon of diabetes management. The frequency of acute complications greatly diminished; but due to the short duration of action it was difficult to achieve good glycemic control round the clock. The picture improved with the discovery of Protamine insulin in 1936 by Hans Christian Hagedorn, followed by NPH insulin in 1946 and Lente insulins in 1952. The commercially available insulins were mostly bovine or porcine in origin till 1980, when rDNA origin human insulin became available. Currently available insulin preparations can be divided into two types- conventional insulins (having the same amino acid sequence as human insulin) and insulin analogues (where a specific change has been made in the amino acid sequence to favorably alter its pharmacokinetics). Conventional insulins may be short acting or intermediate acting according to their duration of action; for the insulin analogues they are rapid acting or long acting[4]. Insulin analogues mimic the physiologic insulin secretion pattern (i.e. maintenance of a peak-less basal insulin level throughout the day by basal analogues, and peaks of bolus insulin during mealtime that perfectly match the post meal glucose excursions). [Table 1]

Table-1: Types of insulin [5].

Insulin Type	Onset of Action	Peak	Duration of Action	Appearance
Bolus (prandial) insulins				
Rapid-acting insulin analogues				
• Insulin Aspart	10-15 min	1-1.5 hour	3-5 hours	Clear
• Insulin Glulisine	10-15 min	1-1.5 hour	3-5 hours	Clear
• Insulin Lispro	10-15 min	1-2 hours	3.5-4.75 hours	Clear
Short-acting (Regular) insulins	30 min	2-3 hours	6.5 hours	Clear
Basal insulins				
Intermediate -acting (NPH)	1-3 hours	5-8 hours	Upto 18 hours	Cloudy
Long-acting insulin analogues				
• Insulin Detemir	90 min	N/A	24 hours	Clear
• Insulin Glargine	90 min	N/A	24 hours	Clear
• Insulin Degludec			42 hours	Clear

There are some distinct advantages of insulin analogues over the conventional insulins, like greater mealtime flexibility, less absorption variability, peak-less profile of basal insulin minimizing the risk of hypoglycemia, and less chance of early post-meal hyper and late post meal hypoglycemia by the rapid acting bolus insulins. Indeed, the insulin analogues mimic the normal physiology most precisely [6].
There are different regimes for insulin administration (Table-2), which are applicable for subcutaneous insulin administration only. In some specific situations, intravenous administration of regular short acting or rapid acting analogue insulin is required; similar are also applicable during insulin pump use.

Table-2: Different types of Insulin Regimen [7].

Regimen	Description
Once daily	NPH or Basal analogue
Twice daily	
• Premixed • Co-formulation • Split-mixed	Less mealtime flexibility
Multiple daily injections • Basal plus	Offers more mealtimeflexibility One long acting analogue at bedtime, plus one injection of rapid acting analogue with the largest meal
• Basal bolus	One long acting analogue at bedtime, plus two or three injections of rapid acting analogue with meal
Continuous subcutaneous insulin infusion	Insulin pump

Table-3: Comparison of different insulin regimes.

Types of Insulin Regimen	Compliance	Cost	Self management education	Monitoring	Need for Care giver facilities	Chance of hypoglycemia	Flexibility
Conventional							
Premixed	(+)	Average	Easy	(++)	(+++)	(+++)	(-)
Split-mixed	(-)	Average	Complicated	(++)	(++)	(+)	(+)
Analogue							
Premixed	(+)	High	Easy	(+)	(++)	(++)	(-)
Co-formulation	(+)	High	Easy	(+)	(+)	(+)	(+)
Basal only	(++)	High	Easy	(+)	(++)	(-)	(+)
Basal-bolus	(-)	High	Easy	(++)	(+)	(-)	(++)

The selection of type and regime of insulin is individualized [Table 3] depending upon particular clinical scenario (type of diabetes, glycemic status, hypoglycemia, glycemic variability, presence of complications and comorbidities) and patient's perspective (compliance, diabetes self-management education, socioeconomic condition, availability). It is the responsibility of the physician to consider all the relevant factors before choosing the appropriate regime for a particular individual. In this context, we can recapitulate the ever memorable quote by Elliott Joslin,"Insulin is a remedy primarily for the wise and not for the foolish. Everyone knows it requires brains to live long with diabetes, but to use insulin successfully requires more than brains" [8].

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Section 2:

Insulin Delivery Devices, Technique and Storage

Key Points:

- *Plastic fixed-needle syringes designed for single use are available in different sizes (U100, U40).*
- *Pen injector devices have been designed to make injections easier and more flexible.*
- *An insulin pump for CSII is an alternative to treatment with MDI. Sensor-augmented pumps are provided with CGM system.*
- *Insulin injections are usually given into the deep subcutaneous tissue at 45-90 degree angle by two-finger pinch of skin. A wait of 15 seconds after pushing in the plunger helps to ensure complete expulsion of insulin.*
- *Sites of insulin injections are: Abdomen (around umbilicus, the preferred site for faster and uniform absorption and less affected by muscle activity or exercise), lateral aspect of thigh, lateral aspect of arm and lateral upper quadrant of the buttocks.*
- *Insulin must never be frozen; direct sunlight or warming should be avoided.*
- *Insulin should not be used if there is change in appearance. Unused insulin should be stored in a refrigerator (4-8^0 C).*
- *When in use, the insulin may be kept in room temperature but it retains its potency much better if kept in refrigerator.*
- *In hot climates where refrigeration is not available, cooling jars, earthenware pitcher or a cool wet cloth around the insulin vials/pens will help to preserve insulin activity*

1. Insulin delivery devices

1.1.: Insulin syringe

Plastic fixed-needle syringes are available in different sizes (U100, U40). These syringes are designed for single use. However, many individuals reuse them without significant risk of infection [1]. Patient can change it every 3-4 days interval if adequate hygiene can be maintained.

1.2.: Pen injector device

Pen injector devices containing insulin in pre-filled cartridges have been designed to make injections easier and more flexible.The dose is dialed up and then pushed. These are available in reusable (cartridges can be replaced when required) or one-time use devices. Needle is to be changed every 3-4 days intervals or when tip becomes blunt.

1.3.: Continuous subcutaneous insulin infusion (CSII)

An insulin pump is an alternative to treatment with MDI. The pump is worn at waist or other convenient places, and insulin is delivered through tube into subcutaneous needle placed over

abdomen. Basal insulin is delivered continuously, and the bolus dose is person-activated. Rapid acting insulin analogues are usually used in these devices, both as basal as well as bolus dose.

Sensor-augmented pumps are provided with CGM system. Newer generation pumps automatically shut-off to prevent hypoglycemia when the sensor has fallen below a preset threshold. The newer smart pumps can automatically calculate meal or correction boluses based on insulin-to-carbohydrate ratios and insulin sensitivity factors.

2. Injection technique

2.1.: Injections are given into the deep subcutaneous tissue at 45-90^0 angle by two-finger pinch of skin.The pinch is recommended to ensure a strict subcutaneous injection; avoiding intramuscular injection. Injections can be given perpendicularly without lifting a skin fold when needles are smaller and there is enough subcutaneous fat.The needles should be inserted fully, otherwise there is a risk of intradermal injections. A wait of 15 seconds after pushing the plunger helps to ensure complete expulsion of insulin through the needle, especially in pens [2]. Cleaning or disinfection of skin is advisable, but may not be necessary unless hygiene is a real problem [3,4].

2.2.: Vials (also the pen devices) of cloudy insulin must always be gently rolled (not shaken) 10-20 times, to mix the insulin suspension. When a mixture of two insulins drawn up (e.g. regular insulin are mixed with NPH), the regular insulin is to be drawn up into the syringe before the intermediate acting one. The mixture must be administered immediately.

3. Injection sites [5,6]:

3.1.: Abdomen (the preferred site when faster and uniform absorption is required and it may be less affected by muscle activity or exercise).

3.2.: Lateral aspect of thigh (the preferred site for slower absorption of longer acting insulin).

3.3.: Lateral aspect of arm (assistance is required for injection).

3.4.: The lateral upper quadrant of the buttocks (used less often).

3.5.: Rotation of injection sites are important within the same area of injection.

4. Storage of insulin

4.1.: Insulin must never be frozen.

4.2.: Direct sunlight or warming (e.g. in hot climates) damages insulin.

4.3.: Insulin should not be used if there is change in appearance (clumping, frosting, precipitation, or discoloration).

4.4.: Unused insulin should be stored in a refrigerator(4-8^0 C) to retain its potency up to expiry date.

4.5.: When in use, the insulin may be kept in room temperature (if not too hot) without much loss of efficacy. But it retains its potency much better if kept in refrigerator.

4.6.: In hot climates where refrigeration is not available, cooling jars, earthenware pitcher [7] or cool wet cloth around the insulin will help to preserve insulin activity.

4.7.: After first usage, an insulin vial should be discarded after a certain period as instructed by manufacturer.

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Section 3:

Insulin Initiation and Intensification in DM

Key points:

- *Insulin should be initiated in T2DM patients with HbA1c ≥ 10%, symptomatic hyperglycemia ± ketonuria, PPG > 19.4 mmol/L, FPG> 16.6 mmol/L, if the glycemic targets are not achieved by using three non-insulin agents by at least 3 months, during acute illness, surgery, stress, emergencies, pregnancy and lactation, as initial therapy in T2DM with severe hyperglycemia, severe metabolic decompensation (eg. DKA, HHS), and T1DM.*
- *Insulin regimens are: Basal alone, Basal plus, basal bolus, split-mixed, pre-mixed, co-formulation, combination with injectable agents.*
- *Initiation can be done by basal insulin with the dose of 10 units or 0.1-0.2 U/kbw. While with split-mixed or pre-mixed regimen, insulin may be intiated at dose of 0.2-0.3 U/kbw. Intensification should be done with increase of 10-20% of dose or 2-4 units of insulin as per SMBG records once or twice weekly until glycemic targets are achieved.*
- *Switching should be done from one regimen to other one when appropriate.*
- *Basal bolus regimen (MDI) is preferred than pre-mixed regimen in T1DM.*
- *In children and adolescent MDI, CSII or 1-3 dose of bolus insulin regimen can be chosen.*

A.: Insulin Initiation and Intensification in Type 2 DM

1.: Indication of using insulin in T2DM: [1]

Insulin should be initiated in Type 2 DM in following conditions:

- HbA1c ≥ 10%
- Symptomatic hyperglycemia ± ketonuria.
- PPG > 19.4 mmol/L, FPG> 16.6 mmol/L.
- If the glycemic targets are not achieved by using three non-insulin agents (metformin/pioglitazone, secretagogue, αGi/DPP4i/SGLT2i) by at least 3 months.
- In some specific situations: Short term use of insulin therapy in patients with T2DM may also be considered in the following conditions: acute illness, surgery, stress and emergencies, pregnancy and lactation.
- Severe metabolic decompensation (eg. DKA, HHS).

2.: Insulin Therapy

Many patients with type 2 diabetes eventually require and get benefit from insulin therapy. The progressive nature of type 2 diabetes should be explained to patients frequently. Equipping patients

with an algorithm for self-titration of insulin doses based on self-monitoring of blood glucose (SMBG) improves glycemic control in patients with type 2 diabetes. Comprehensive education regarding SMBG, diet and the avoidance of and appropriate treatment of hypoglycemia are critically important in any patient using insulin[1].

2.1.: Basal Insulin

2.1.a.: Initiation

Basal insulin is preferably better to start if A1C is > 9.0% in newly detected diabetes or in an old patinet of type 2 diabetes. Basal insulin alone is the most convenient initial insulin regimen, beginning at 10 units per day or 0.1–0.2 units/kg/day, depending on the degree of hyperglycemia. Basal insulin is usually prescribed in conjunction with metformin and sometimes one additional noninsulin agent[1].

2.1.b.: Adjustment

Adjust basal insulin by 10-15% or 2-4 U once-twice weekly to reach FPG target (at least 3 days apart). In case of hypoglycemia determine and address cause (s); reduce dose by 4 U or 10-20% of the current dose [1].

2.1.c.: Follow up

After 3 month A1C should be done to evaluate the attainment of glycemic target [1].

2.2.: Basal Plus Insulin

2.2.a.: Initiation

When FPG target is reached or if the dose of basal insulin> 0.5 U/kg/day, treat the PPG excursion with meal time insulin. The ideal meal time insulin is the rapid acting one (aspart, lispro and glulisine). In Bangladesh, the largest meal is usually lunch. So, start: 4 U [or 0.1 U/kg or 10% basal dose] before lunch[1].The short acting human insulin might be used if rapid acting insulins are not available (with increased chances of hypoglycemia).

2.2.b.: Adjustment:

The premeal insulin (rapid acting analogue/ short acting human insulin) dose should be increased by 1-2 U or 10-15% once to twice weekly until SMBG targets are reached.

2.2.c.: Follow up:

If hypoglycemia occurs, determine and address cause(s) and if there is no clear reason(s) causing hypoglycemia, the corresponding dose should be reduced by 2-4 U or 10-20%[1].

2.3.: Basal Bolus Insulin

Many individuals with type 2 diabetes may require mealtime bolus insulin (before 2 or 3 major meals) in addition to basal insulin. Rapid acting analogs are preferred due to their prompt onset of action. If the current A1C of the patient (newly detected patient or already on OADs/ other drugs) is > 10%, basal bolus insulin should be initiated[1].

2.3.a.: Initiation

The recommended starting dose of mealtime insulin is 4 units or 0.1 U/kg or 10% of the basal dose in patients who are on basal insulin.When starting mealtime bolus insulin, consideration should be given to decrease the basal insulin dose.

In insulin naïve patients, the starting dose of basal insulin and bolus insulin typically should be 50: 50.The daily dose may be 0.1 to 0.2 U/Kg of body weight.The ½ of the total daily dose should be allocated at fixed time, preferably at night as basal insulin. The premeal bolus insulin will be divided into 3 nearly equal doses and be taken before each major meals.

2.3.b.: Adjustment:

Increase dose(s) by 1-2 units or 10-15% once or twice weekly to achieve SMBG target.
Two types of insulin should not be titrated at a time. Firstly FPG may be targeted then PPG.

2.4.: Split Mixed Insulin

Two times NPH and 2 or 3 times premeal short acting insulin may be given as an alternative to basal bolus/ premixed/co-formulation insulin. This regimen may be suitable when frequent titration is intended such as while switching from intravenous insulin to subcutaneous insulin (in DKA, HHS and other parenteral feeding situations).

2.4.a.: Initiation:

In insulin naïve patients, the starting dose of NPH and short acting insulin typically should be 2/3: 1/3. The daily dose may be 0.2 to 0.3 U/Kg of body weight. The 2/3 of the total daily dose [which may be for a 70 kg adult patient of type 2 diabetes (70× 0.3= 21, 2/3 of that = 14 U)] should be allocated as NPH; 2/3rd of the NPH dose should taken 30 minutes before breakfast and 1/3rd 30 minutes before dinner. The short acting insulin will be divided in to 2 or 3 nearly equal doses and be taken before each major meals (4U+0+4U or 2U+2U+2U or 3U+3U+3U) [2,3].

2.4.b.: Adjustment:

Dose titration will be done by monitoring the SMBG.

2.5.: Premixed Insulin

Premixed insulin products contain both basal and prandial component, allowing coverage of both basal and prandial needs with a single injection. NPH/regular 70/30 insulin, for example, is composed of 70% NPH insulin and 30% regular insulin. These may also contain 75/25, 50/50 ratios of NPH/regular insulins.

There are analogue premixed insulins containing different proportions of intermediate acting and rapid acting insulin e.g.; 70/30 aspart mix, 75/25 or 50/50 lispro mix).Co-formulation insulin analogue insulin contains 70/30 ratio of degludec/aspart. Each approach has its advantages and disadvantages.

2.5.a.: Initiation and Titration of Premix insulin

Premix insulin can be started once daily with 10U or 0.3U/kbw either in the morning (AM), if night time / pre-dinner glucose is high or in the night (PM), if the morning glucose (FPG) is high. If the total

insulin dose exceeds 20 U, then premix insulin can be given twice daily, before breakfast and before dinner (AM & PM), distributed as two third in morning and one third in evening.

Premix analogues/ co-formulation insulin should be distributed in two equal halves in morning and evening when single dose exceeds 30 units. Also premix insulin may be started twice daily in case of patients with higher HbA1c, or if FPG and PPG both are suboptimal.

The simple principle of "starting low and scaling slow" must be applied.

2.5.b.: Monitoring procedure while on Premix insulin

Premix insulin can be given once daily before breakfast or dinner. Then it can be intensified to twice or thrice (pre-mixed analogue) daily. Dinner (PM) or morning (AM) dose needs to be titrated based upon pre-breakfast or pre-dinner blood glucose respectively. Titration should be done at regular interval (at least weekly) until glycemic goals are achieved.

2.5.c.: Adjustment:

Suggested titration is 1 to 2 units added to pre-breakfast dose and/or pre-dinner dose every 3 days interval until target BG values are reached.Pre-breakfast premixed insulin achieves pre-dinner target BG value. Pre-dinner premixed insulin achieves target fasting BG value.

Premixed conventional human insulin should be given 30 minutes before meals. Biphasic analogue and co-formulation insulin should be given immediately before meal.

If BG targets are not reached, continue to increase the relevant dose until both targets are achieved. The individual may need to self-monitor BG 2 times a day to safely titrate insulin.

2.6.: Combination Injectable Therapy

If basal insulin has been titrated to an acceptable fasting blood glucose level (or if the dose is>0.5 units/kg/day) and A1C remains above target, consider advancing to combination injectable therapy[Figure 1].

When initiating combination injectable therapy, metformin should be maintained while SU may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e., adding a fourth antihyperglycemic agent). In general, GLP-1 receptor agonists should not be discontinued with the initiation of basal insulin. Sulfonylurea, is typically stopped once more complex insulin regimens beyond basal are used. In patients with sub-optimal blood glucose control, especially those requiring large insulin doses, adjunctive use of a DPP4i, αGi, thiazolidinedione or SGLT2 inhibitor may help to improve control and reduce the amount of insulin needed, though potential side effects should be considered. Once an insulin regimen is initiated, dose titration is important with adjustments made in both mealtime and basal insulins based on the blood glucose levels and understanding of the pharmacodynamic profile of each formulation [4,5].

2.7.: Switching Between Insulin Regimen

2.7.a.: Regular human insulin and human NPH/Regular premixed formulations (70/30) are less costly alternatives to rapid-acting insulin analogues, premixed insulin analogs and co-formulation. But their pharmacodynamic profiles may make them less optimal and frequent hypoglycemic events may hamper treatment adhrenece.

2.7.b.: Consider switching patients from one regimen to another (i.e., premixed analog insulin three times daily to basal- bolus regimen or vice-versa) if A1C targets are not being met and/or depending on other patient considerations(willing to reduce injection frequency, care giver dependency, when frequent monitoring of BG is not possible).

2.7.c.: Self-monitoring of blood glucose (SMBG) can be helpful in determining appropriate targets for therapy. It is useful to monitor responses to therapy and to identify and treat glycemic excursions above or below target levels. Clinical experience suggests that SMBG is an important component of effective therapy.

2.7.d.: Switching from Basal to Premixed regimen

For those patients on combination OADs and basal insulin not achieving HbA1c targets despite optimal FBG, with post-prandial hyperglycemia,another option for intensification would be to switch to a premixed regimen[6,7].

This option is usually appropriate for patients who prefer a simpler regimen and are unable to accept 3 – 4 injections per day. This regimen is more suitable for those with a rigid lifestyle. Sulphonylureas should be stopped but metformin should be continued.

Dose for dose transfer can be used where the total daily dose of basal insulin is used to determine total daily dose (TDD) of premixed insuln. TDD is then administered in two divided doses, usually equal in amount ie: split dose 50: 50 at pre-breakfast and pre-dinner [6].

2.7.e.: Switch from basal bolus to premixed twice daily

- *Total dose transfer should be done.*
- *Split dose 50:50 ratio [pre-breakfast : pre-dinner]*
- *Titrate dose once or twice a week to reach pre-breakfast or pre-dinner BG targets.*
- *Stop SU, continue metformin*
- *Consider premixed analogue insulin.*

Premixed analogues, co-formulation may be considered in patients experiencing hypoglycaemia with conventional premixed insulin and in those who desire greater flexibility as administration of premixed analogue does not require specific timing prior to meals and may be injected just prior to, during, or immediately after a meal.

2.7.f.: Switching from Premixed to Basal bolus regimen:

For those patients on premixed regimen (twice or three times daily) and not achieving HbA1c targets despite optimised dose, another option for intensification would be to switch to basal-bolus regimen.

This option is appropriate for patients who require greater flexibility in dose adjustment as it potentially allows pre-meal rapid / short-acting insulin to be adjusted individually according to blood glucose level (correctional bolus) along with the carbohydrate meal content of the meal.

The initial total daily dose following the switch may be guided by using a simple dose calculation of 0.5units/kg or by a total dose for dose transfer from the prior total daily dose on the previous regimen. Following determination of total daily- dose requirement, proportion of basal to prandial insulin requirement may be estimated using a ratio of 50:50. A smaller proportion of basal insulin may also be used such as between 25 – 40% of total daily dose in certain circumstances. The basal dose is usually administered at bedtime (conventional insulin or analogue) and the prandial portion is divided into three equal doses to cover the three main meals. Estimation of the pre-meal dose should take into consideration prdins to the size of the meal, in terms of the carbohydrate content. Subsequently the basal and pre-meal insulin should be titrated or optimised accordingly towards attaining glycemic targets[6].

2.7.g.: Switching from single to multiple premixed regimen

For those patients already on a single premixed insulin regimen, usually in combination with single or multiple OADs and not achieving blood glucose and HbA1c targets despite optimising insulin and OAD doses, an option for intensification would be to initiate additional pre-meal doses of premixed insulin.

For those on single dose premixed insulin, usually prior to evening meals, one additional dose may be initiated prior to the morning meal or split the dose 50:50 to breakfast and dinner. In those receiving premixed analogue insulin, additional dose may be initiated at both morning and midday- meals, either sequentially or simultaneously. It is not usual to administer conventional premixed insulin more than twice daily in view of concern for between-meal hypoglycaemia[8-11].

B.: Insulin Initiation and Intensification in Type 1 Diabetes

3.: Adults with type 1 diabetes

3.1.: Rather than twice daily mixed insulin regimens, offer basal bolus insulin regimens (MDI), as the insulin injection regimen of choice for all adults with type 1 diabetes[11].

3.2.: Long acting insulin

Twice daily NPH, detemir, glargine or once daily glargine, degludec may be considered as basal insulin therapy for adults with type 1 diabetes.

3.3.: Rapid acting insulin

Offer rapid acting insulin analogues before meals, rather than short actions human insulins, for mealtime insulin replacement for adults with type 1 diabetes. Do not advise routine use of rapid acting insulin analogues after meals.

3.4.: Split Mixed Insulin

Thrice daily human insulin regimen (two times NPH and 3 times premeal short acting insulin) for adults with type 1 diabetes is recommended if an MDI basal-bolus insulin regimen is not possible. Consider twice daily analogue mixed insulin regimen if hypoglycemia is an issue.

4. Children and young people with diabetes

4.1.: While the insulin regimen should be individualized for each patient, there are three basic types of insulin regimen:1. MDI basal-bolus insulin regimens: once daily injection of long acting insulin analogue and three rapid-acting insulin analogue before meals which is the preferred insulin regimen. 2. CSII therapy: a programmable pump and insulin storage device that gives continuous infusion of insulin (usually a rapid acting insulin analogue or short acting insulin) by a subcutaneous needle or cannula. 3. One, two or three insulin injections per day: these are usually injections of short acting insulin mixed with intermediate acting insulin.

4.2.: For children and young people with type 1 diabetes, MDI basal-bolus insulin regimens should be considered from diagnosis. If an MDI regimen is not appropriate for a child or young person with type 1 diabetes, consider CSII therapy [11]. For children of less than 1 year of age, degludec is not recommended.

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Section 4:

Insulin Therapy at Hospital Settings

Key Points:

- *For inpatients, best tool to differentiate between stress hyperglycemia and pre-existing diabetes mellitus (DM) is A1C. A value of A1C ≥6.5% suggests pre-existing DM.*
- *Target plasma glucose during hospital stay at intensive care unit is in between 7.8 mmol/L to 10.0 mmol/L and at non-icu setting, premeal < 7.8 mmol/L and random/post meal < 10 mmol/L.*
- *Glycemic target is best achieved with judicious use of insulin.*
- *Recommended insulin therapy protocol at non-ICU settings: Subcutaneous basal insulin ± prandial insulin ± correction insulin regimen. Sliding scale insulin (SSI) regimen is not recommended. Premixed insulins can be used for stable persons or before discharge.*
- *Naso-gastric (NG) tube feeding/ Per-enteral tube feeding: In patients while on per enteral tube feeding, two episodes of feeding should be ensured after the evening prandial S/C insulin to avoid nocturnal hypoglycemia.*
- *Recommended insulin therapy protocol at ICU settings: Short acting regular insulin in IV route is recommended to be use by IV infusion pump device at rate of 0.5 to 12 units/ hour. Another approach is weight-based calculation of insulin dose e.g.; 0.01 to 0.02 to 0.05 units of insulin/Kg body weight/hour.*
- *Peri-operative insulin therapy: Perioperative PG target is between 6.0 – 10.0 mmol/L. At night before the intended procedure, regular insulin regimen should be used.*

Mortality and morbidity of patients admitted into hospital are increased with hyperglycemia [1,2,3].At inpatient settings, hyperglycemia is defined as RPG ≥ 7.8 mmol/L. Best tool to differentiate between stress hyperglycemia and pre-existing diabetes mellitus (DM) is A1C. A value of A1C ≥6.5% suggests DM [4]. During hospital stay, target plasma glucose at intensive care unit is in between 7.8 mmol/L to 10.0 mmol/L and at non-ICU setting, premeal < 7.8 mmol/L and random/post meal < 10 mmol/L [4].

In this regard, practical "guideline" is less formulated due to fewer researches, various clinical settings and less experience with newer agents [4,5,6]. We proposes following insulin therapy for treating hyperglycemia in various inpatient settings.

1. Insulin therapy protocol at non-ICU settings:

1.1: In non-ICU settings, physiological insulin replacement protocol in subcutaneous (SC) route is Basal insulin ± Prandial insulin ± Correction insulin regimen when meal consumption is regular.

1.2.: While meal intake is discrete or the patient is on NPO, naso-gastric feeding (NG) and or receiving total par-enteral nutrition (TPN), this regimen is defined as Basal ± Nutritional ± Correction insulin regimen [4,5,6].

1.3: Basal-prandial insulin regimen is superior to sliding scale insulin (SSI) because SSI regimen lacks basal component which is required to suppress and or prevent gluconeogenesis and ketogenesis [7].

1.4: Physiological Insulin replacement protocols in SC route for various inpatients settings are as follow [4,5,6]:

- **Step 1:** Define nutritional status of patient, that is whether patient is eating or under settings of NPO, tube feeding, TPN, etc.
- **Step 2:** Then, estimate approximate total daily dose (TDD) of insulin. One approach is to take history of previous total dose, current A1c and adjust the dose accordingly. When records are not available or patient is insulin naïve, another approach is weight-based calculation of TDD of insulin as following; TDD of insulin: 0.3 to 0.5 units of insulin/kg body weight/Day.
- **Step 3:** Split TDD of insulin into basal and prandial/ nutritional components as 50/50 or 30/70 ratio. NPH, long acting basal analogues insulins are used as basal component and short acting regular or rapid acting analogues insulins are used as prandial/ nutritional component in SC route.

  Example: A 70 kg diabetic male with random plasma glucose of 12 mmol/L and A1c 7.2% is admitted into general medicine ward. Patient can take meal routinely. Before admission he was on premixed (30/70) insulin at a dose 24+0+20 SC. So, his TDD of insulin is 24+20=44. Now, split TDD into 30% basal (e.g.; 15 units basal analogue given SC once or 7 units NPH twice daily) and into 70% prandial component (e.g.; 70% of 44= 30 units; so 10 units regular short acting/ rapid acting analogue given SC 3 times before 3 major meals).
- **Step 4:** Correction or supplement dose is given with regular short acting or rapid acting analogue insulin in SC route which may be required if pre-meal PG is high. After 24 hour plasma glucose monitoring (pre-meals, 2 hour post-meals, q 4-6 hourly), re-adjust the dose. The regimen should be re-assessed on daily basis depending on plasma glucose level and condition of patient. Detailed protocol in various settings are mentioned in Table 1.

1.5.: Naso-gastric (NG) tube feeding/ Per-enteral tube feeding: In patients on per enteral tube feeding, two feeding should be ensured after the evening prandial S/C insulin to avoid nocturnal hypoglycemia.

2. Insulin therapy protocol at ICU settings:

2.1: Insulin in intravenous (IV) route is used in these settings, e.g.; MICU, SICU, major Surgery, cardiovascular procedures, MI, NPO, DKA, high dose steroids, gastroparesis, dose finding strategy etc [5].

2.2: Short acting regular insulin in IV route is used by infusion pump device in these settings. As per PG values, infusion rate may vary between 0.5 to 12 units of insulin/ hour. Another approach is weight based calculation of insulin dose e.g.; 0.01 to 0.02 to 0.05 units of insulin/Kg body weight/hour [5,8].

2.3: Switching from IV insulin to SC insulin regimen [4,5,6]:

- **Step 1:** first find out TDD of insulin which may be required by patient in next 24 hours. This is best calculated by following formula: TDD of insulin for next 24 hours= Stabilized hourly rate of insulin x 20. For example, if patient and his PG were stable with 2 units/ hour of regular short acting insulin then TDD requirement for next 24 hours would be approximately 2x 20= 40 units of insulin.
- **Step 2:** Then, divide TDD of insulin into 30-50 % basal insulin and 70 to 50% into 3 prandial/nutritional insulin components. SC insulin should be started 1-2 hour before discontinuation of IV insulin. Correction dose with short acting of insulin may be required. Re-assess the regimen and dose after 24 hours and re-adjust as required.

3. Peri-operative insulin therapy [4,5,6]:

3.1: At perioperative period, PG target is between 6.0 – 10.0 mmol/L.

3.2: Surgical procedure is encouraged to be started at early morning. At night before the intended procedure, regular insulin regimen should be used.

3.3: At morning, during short procedures, ½ of NPH or long acting basal insulin in SC route is given and PG is monitored every 30-60 minutes interval and if PG is above target then correction dose with regular short acting insulin or rapid acting analogue insulin in SC route should be administered Q 4-6 hourly.

3.4: During prolonged procedures, IV infusion of 5% dextrose + IV short acting regular insulin in drip is used with SC correction dose of regular short acting insulin or rapid acting analogue insulin Q 4-6 hourly if needed. Fluid balanced should be maintained.

4. Use of Pre-mixed insulin:

Premixed insulins can be used for stable persons or before discharge [4,6].

Table 1: Physiological Insulin replacement protocols for various inpatient settings [5]

Settings	TDD of insulin	Basal insulin S/C q 24 or 12 h Basal–I or NPH	Prandial / Nutritional insulin S/C q 4-6 h Reg-I, Rapid-I	Correction*/ Supplement dose S/C insulin with Reg-I, Rapid-I	IV insulin
On insulin therapy-Eating	0.4-0.6 U/Kg/day	30%-50 %	70-50%	Pre-meal over 10 mmol/L for 1 mmol/L =0.5-1 unit I	
On insulin therapy-NPO	0.4-0.6 U/Kg/day	30%-50 %	70-50%	Same	Insulin drip Reg I 1-4 U/100ml of 5% DNS at 75-100 ml/hr

Previous Oral agents-Eating	0.3 U/kg/day	30%-50 %	70-50%	Same	
Previous Oral agents- NPO	0.3 U/kg/day	20% - 50%	80-50%	Same	Insulin drip Reg I 1-4 U/100ml of 5% DNS at 75-100 ml/hr
Newly diagnosed hyperglycemia –eating	0.3U/kg/day	30%-50%	70-50%	Same	
Newly diagnosed hyperglycemia –NPO	0.2U/kg/day	Basal+/-		Same	Insulin drip Reg I 1-4 U/100ml of 5% DNS at 75-100 ml/hr
Enteral tube feeding	0.3U/kg/day	<40%:	>60%	Same	
On Steroid	0.4-0.6 U/kg/day	30%-50 %	70-50%	Same	Insulin pump may be requied

N.B.; TDD: total daily dose of insulin; U: unit; Kg: kilogram; I: insulin; Reg I: regular short acting insulin; Rapid I; rapid acting analogue insulin; NPH: Neutral Protamine Hagedorn;.

*Another approach of Correction Insulin dose calculation: 1. Correction Factor (CF) is calculated by dividing the constant 1700 by TDD of rapid acting insulin or dividing 1500 by TDD of short acting insulin. 2. then, calculate Correction Insulin dose =(Current BG -Target BG in mg/dl) / CF. [9]

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Section 5:

Insulin Therapy in Hyperglycemic Crises

Key points:

- *Acute metabolic hyperglycemic complications of diabetes are Diabetic ketoacidosis (DKA) and the Hyperosmolar Hyperglycemic State (HHS).*
- *The combination of uncontrolled hyperglycemia, anion gap, metabolic acidosis, and ketonemia/ketonuria characterizes DKA.*
- *HHS is characterized by severe hyperglycemia, hyperosmolality, and dehydration in the absence of significant ketoacidosis.*
- *The most common precipitating factor in the development of DKA and HHS is intercurrent infection; other precipitating factors include discontinuation of insulin therapy, inadequate insulin therapy, pancreatitis, myocardial infarction, cerebrovascular accident, new-onset type 1 diabetes, pulmonary embolism, psychological problem etc.*
- *The principles of treatment of DKA and HHS includes- correction of dehydration, hyperglycemia, electrolyte imbalances and identification of comorbid precipitating events along with frequent patient monitoring.*
- *Continuous administration of short acting regular insulin via intravenous infusion is the mainstay and preferred route because of its short half-life and easy titration.*

Serious acute metabolic complications of diabetes are diabetic ketoacidosis (DKA) and the hyperosmolar hyperglycemic state (HHS). In the USA, DKA is responsible for more than 500,000 hospital days per year [1,2]. The combination of uncontrolled hyperglycemia, metabolic acidosis, and ketonemia/ketonuria characterizes DKA. HHS is characterized by severe hyperglycemia, hyperosmolality and dehydration in the absence of significant ketoacidosis. Table 1 outlines the diagnostic criteria for DKA and HHS. These metabolic derangements result from the combination of absolute or relative insulin deficiency and an increase in counter-regulatory hormones (glucagon, catecholamines, cortisol and growth hormone). Majority of the patients with DKA belong to type 1 diabetes. However, patients with type 2 diabetes can also develop DKA during stress and acute illness such as trauma, surgery, or infections.

Diabetic ketoacidosis is the most important cause of death in children with type 1 diabetes. It accounts for half of all deaths in diabetic patients younger than 24 years of age [3,4]. The overall mortality in adult subjects with DKA may be as low as<1% [1], but the rate is higher (~5%) in the elderly and in patients with concomitant life-threatening illnesses [5,6]. Mortality due to HHS is considerably higher (5–20%) [7,8].

1. Pathophysiology of DKA and HHS:

1.1.: The principal mechanism of hyperglycemia and ketosis in DKA is reduced effective insulin concentrations and increased concentrations of counter regulatory hormones. Due to lack of insulin, free fatty acids are released into the circulation from adipose tissue (lipolysis). There is unrestrained hepatic fatty acid oxidation in the liver to ketone bodies, resulting in ketonemia and metabolic acidosis [9].

1.2.: In HHS, there is a greater degree of dehydration, but endogenous insulin secretion is more than in DKA. In HHS insulin level is inadequate to counteract hyperglycemia but adequate to prevent lipolysis and subsequent ketogenesis [10].

2. Precipitating Factors of DKA & HHS:

2.1.: The most common precipitating factor in the development of DKA and HHS is intercurrent infection [1,7].

2.2.: Other precipitating factors include discontinuation of insulin therapy, inadequate insulin therapy, pancreatitis, myocardial infarction, cerebrovascular accident, pulmonary embolism, new-onset type 1 diabetes.

2.3.: Psychological problem is an important contributing factor for recurrent ketoacidosis in young patients with diabetes.

3. The principles of treatmentof DKA and HHS:

- Correction of dehydration
- Correction of hyperglycemia
- Correction of electrolyte imbalances
- Identification of comorbid precipitating events
- Frequent patient monitoring.

3.1.: Administration of regular insulin via continuous intravenous infusion is the mainstay in the treatment of DKA [11]. Insulin therapy is effective regardless of the route of administration [12]. However, continuous administration of insulin via intravenous infusion is the preferred route because of its short half-life and easy titration [12,13,14].

3.2.: At the beginning patients should receive an hourly insulin infusion of 0.1 units/kg body weight [15]. The target is to decrease plasma glucose concentration at a rate of 3-6 mmol/L/hour. If plasma glucose does not decrease by 3-6 mmol from the initial value in the first hour, the insulin infusion should be increased every hour until a steady glucose decline is achieved (Figure 1). When the plasma glucose reaches 13.8 mmol/L in DKA or 16.7 mmol/L in HHS, it may be possible to decrease the insulin infusion rate to 0.05-0.1 units/kg/hour, at which time dextrose may be added to the intravenous fluids. Thereafter, the rate of insulin administration or the concentration of dextrose may need to be adjusted to maintain glucose values between 8.3 and 11.1 mmol/L in DKA or 11.1 and 16.7 mmol/L in HHS until they are resolved [16].

3.3.: The continuous intravenous insulin infusion in patients with DKA/HHS should be continued until the hyperglycemic crisis is resolved. Criteria for resolution of ketoacidosis includes a blood glucose<11.1 mmol/L and two of the following criteria:

- Serum bicarbonate level >15mEq/l
- Venous pH >7.3
- Calculated anion gap<12 mEq/l.

3.4.: Resolution of HHS is indicated by normal plasma osmolality and regaining normal mental status. When resolution occurs, subcutaneous insulin therapy can be started. To prevent recurrence of hyperglycemia or ketoacidosis during the transition period to subcutaneous insulin,it is important to allow an overlap of 1–2 hours between discontinuation of intravenous insulin and the administration of subcutaneous insulin. The intravenous insulin infusion and fluid replacement should be continued despite biochemical resolution of the crises if the patient is to remain fasting/nothing by mouth. Patients with known diabetes may be given insulin at the dosage they were receiving before the onset of DKA if it was controlling glucose properly [16]. In insulin-naïve patients,a multi dose insulin regimen should be started at a dose of 0.5 - 1.0 units /kg/ day [19]. Human insulin (NPH and regular) may be given in two or three doses per day. However, basal-bolus regimen is the best option as it efficiently mimics physiologic insulin secretion. Table-2 shows a proposed method for estimation of insulin dose while switching from intravenous to subcutaneous insulin [20].

Table-1: Diagnostic criteria for DKA and HHS [16].

	DKA			HHS
	Mild	**Moderate**	**Severe**	
BG	>13.8 mmol/L	>13.8 mmol/L	>13.8 mmol/L	>33.3 mmol/L
Arterial PH	7.25-7.30	7.00 to<7.24	<7.00	>7.30
Serum Bicarbonate (mEq/L)	15-18	10 to <15	<10	>18
Urine Ketone	Positive	Positive	Positive	Small
Effective serum osmolality	Variable	Variable	Variable	>320 mOsm/Kg
Anion gap	>10	>12	>12	Variable
Mental status	Alert	Alert/Drowsy	Stupor/ Coma	Stupor/ Coma

Effective serum osmolality= 2 [measured Na^+ (mEq/L)] + Glucose (mmol/L)

Anion gap= (Na^+) – [Cl^- + HCO3 (mEq/L)]

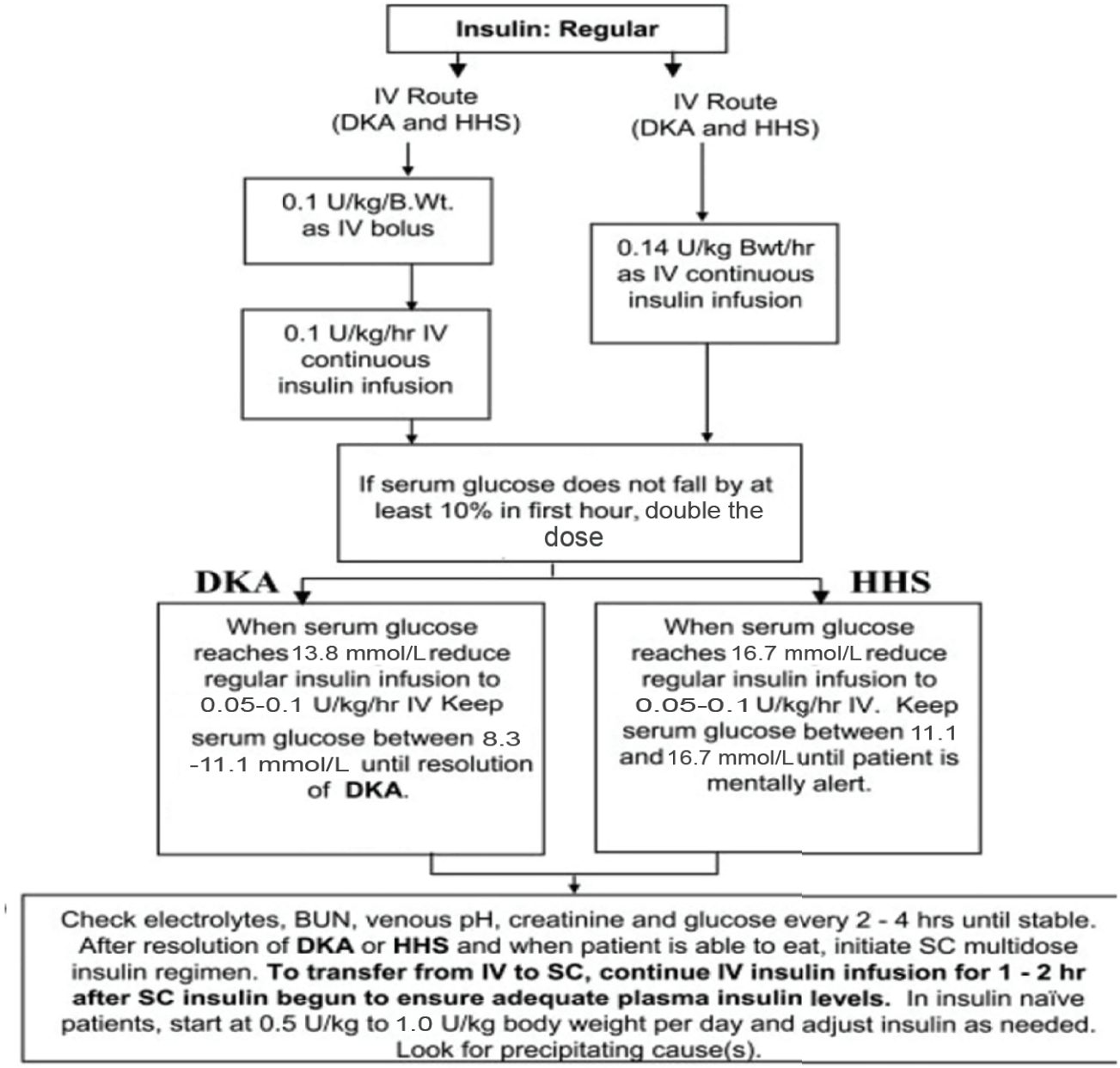

Table 2: Estimation of insulin dose (S/C) for a patient being converted from an intravenous insulin infusion [20].
• Calculate average hourly insulin dose by totaling the last 6 hours doses on the chart and dividing by 6 (e.g. 15 units divide by 6 = 2.5 units/hour. Multiply by factor of 20 to get the total daily dose (TDD) insulin (e.g. 50 units)
• For a basal : bolus insulin regimen, divide 50 : 50 basal : bolus (e.g. 25 units as basal; 25 units as bolus. Give 25 units as a basal insulin. Divide total bolus dose by three to get bolus for each meal (e.g. 8 units short - acting insulin)
• For a twice daily fixed mixture regime divide 70 : 30 morning : evening.

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Section 6:

Using Insulin During Ramadan Fasting

Key points:

- *During Ramadan fast, person with diabetes can be categorized having very high, high or moderate/low risk.*
- *Pregnant women with diabetes are stratified as very high risk and are advised not to fast.*
- *During Ramadan, use of insulin analogues are better choice over regular human insulin due to a number of advantages.*
- *Structured Ramadan focused education program, pre-Ramadan assessment, appropriate adjustment of treatment and education on meal, exercise should ideally be done 6–8 weeks before the start of Ramadan.*
- *Insulin dose should be reduced at Suhoor to avoid hypoglycemia.*
- *SMBG should be practised frequenty to avoid hypo or hyperglycemia.*

Appropriate dose adjustment and choosing tailored insulin regimen is crucial for people having diabetes who wish to fast during the holy month of Ramadan [1, 2]. During Ramadan fast, person with diabetes can be categorized having very high, high or moderate/low risk [3]. Very high-risk group is advised not to fast. Pregnant women with diabetes are stratified as very high risk and are advised not to fast. [3].

1. Insulin treatment for T2DM during Ramadan:

1.1. Insulin regimen for T2DM may include the use of premixed insulin (human & analogue), co-formulation, rapid acting analogue, split-mixed regimen (human), intermediate-acting (human insulin), basal analogue without or with rapid acting analogue(basal plus, basal bolus regimen) and may be used in conjunction with OADs [4, 5, 6].

1.2. Limited data are available regarding the optimal insulin type or regimen for people with T2DM during Ramadan but results from several studies indicate that appropriate modification and individualization of insulin regimens are required [7, 8, 9, 10, 11, 12].

1.3. During Ramadan, use of insulin analogues is recommended over human insulin due to a number of advantages e.g.; less hypoglycemia, less weight gain, flexibility with meal time [13].

1.4. Pre-Ramadan assessment, appropriate adjustment of treatment, education on meal, exercise and monitoring of blood glucose monitoring should ideally be done 6–8 weeks before the start of Ramadan [3].

1.5. Patients with T2DM with poor glycaemic control despite of using multiple daily injections (MDI) of insulin can possibly be benefitted from CSII [14].

1.6. The "South Asian Consensus Guideline: Use of insulin in diabetes during Ramadan" states that 'Once- or twice-daily injections of intermediate or long-acting insulin along with pre-meal rapid-acting insulin is the management of choice' [15].

1.7. Recommended dose adjustments and SMBG-guided dose titrations can be found in Tables 1,2 and 3[3, 16]. Dose adjustment while switching from premixed human to premixed analogue insulin and while using insulin pump can be found in Tables 4 and 5. [3, 17, 18, 19].

2. Insulin treatment for T1DM during Ramadan:

2.1. Religious leaders, in alliance with diabetes experts, do not recommend fasting in individuals with T1DM [3, 20]. However, many persons with T1DM choose to fast.

2.2. The decision to fast during Ramadan must be respected and if the person is stable and healthy, he or she can do so with strict medical supervision and focused education [3].

2.3. Recommended insulin dose adjustment for person with T1DM during Ramadan fast can be found in Tables 1, 3, 5 and 6[3].

2.4. Adolescents with T1DM must be aware of all potential risks associated with Ramadan fasting. Insulin dose adjustment can be found in Table 6 [3].

2.5. Capillary blood glucose should be monitored several times during the day [3].

3. Frequency of SMBG during Ramadan:

Recommended schedule are as follow [3]:

3.1. Moderate/Low risk: 1–2 times a day e.g.; 1 or 2 hour before Iftar / 4-6 hour after Suhoor, 2 hour after Iftar/ dinner.

3.2. Very high/ High Risk: several times a day e.g.; 1 or 2 hour before Iftar, 2 hour after Iftar/ dinner, before Suhoor, 4-6 hour after Suhoor.

3.3. Dose titration should be done according to SMBG results every 3rd day or as frequently as required.

4. When to break fast:

Fasting should be broken if any of following conditions arises [3].

4.1. Blood glucose <3.9 mmoI/L (<70 mg/dL).

4.2. Re-check within 1 h if blood glucose is between 3.9–5.0 mmoI/L (70–90 mg/dL).

4.3. Blood glucose >16.7 mmoI/L (>300 mg/dL) or symptomatic.

4.4. Symptoms of hypoglycaemia or acute metabolic complications.

Tables:

Table 1: Pre-mixed (human/ analogue) insulin dose adjustment during Ramadan both in T2DM & T1DM.		
Once-daily dosing	Usual dose at iftar	
Twice-daily dosing	Usual morning/higher dose at iftar.	Reduce evening/lower dose 50% if BG controlled or 0 -25% if BG is uncontrolled and prescribe at suhoor.
Thrice -Daily dosing (analogue)	Usual morning/higher dose at iftar.	Reduce evening/lower dose 50% if BG controlled or 0 -25% if BG is uncontrolled and prescribe at suhoor. Omit lunch -time dose.
SMBG guided dose titration: Should be carried out every 3rd day.		

Table 2: Co-formulation (analogue) insulin dose adjustment during Ramadan.		
Once-daily dosing	Usual dose at iftar	
Twice-daily dosing	Usual breakfast/lunch dose at iftar.	Reduce evening dose 30-50% and prescribe at suhoor.
SMBG guided dose titration: Should be carried out every 3rd day.		

Table 3: Intermediate (NPH)/Long acting (basal analogue) and Short/Rapid (analogue) acting insulin dose adjustment during Ramadan both in T2DM & T1DM.		
NPH/Basal analogue: Once-daily dosing	Reduce dose by 15-30% and prescribe at iftar	
NPH/ Basal analogue: Twice-daily dosing	Usual morning dose at iftar.	Reduce evening dose 50% and prescribe at suhoor.
Short acting insulin/ rapid acting analogue	Usual morning dose at iftar.	Reduce evening dose 50% and omit lunch- dose if dinner is not taken.
SMBG guided dose titration: Should be carried out every 3rd day.		

Table 4: Switching human pre-mixed to analogue premixed insulin dose adjustment during Ramadan		
Once-daily dosing	Reduce 20-30% of morning dose and prescribe at iftar	
Twice-daily dosing	Reduce 20-30% of morning dose and prescribe at iftar	Reduce evening/lower dose 60% and prescribe at suhoor.
SMBG guided dose titration: Should be carried out every 3rd day.		

Table 5: Insulin pump dose adjustment during Ramadan both in T2DM & T1DM.		
Basal rate	Increase dose by 0-30% during early hours after iftar	Reduce dose by 20-40% during last 3-4 hours of fasting
Bolus rate	As per carbohydrate counting and insulin sensitivity principles	

Table 6: Intermediate (NPH)/Long acting (basal analogue) and Short / Rapid (analogue) acting insulin dose adjustment during Ramadan in adolescent T1DM.		
NPH/Basal analogue: Once-daily dosing	Reduce dose by 30-40% and given at iftar	
NPH/ Basal analogue: Twice-daily dosing	Usual morning dose at iftar.	Reduce evening dose 50% and prescribe at suhoor.
Short acting insulin/ rapid acting analogue	Usual morning dose at iftar.	Reduce evening dose 25-50% and prescribe at suhoor, omit lunch-time dose if dinner is not taken.
SMBG guided dose titration: Should be carried out every 3 rd day.		

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Section 7:

Insulin Use in Pregnancy

Key Points:

- *Strict glycemic control is mandatory before and throughout pregnancy in pre-gestational diabetes and during pregnancy in GDM.*
- *Insulin is the standard of care to attain optimal glucose control in pregnancy and multiple methods and regimens are available to initiate insulin.*
- *Insulin therapy should be considered if one fails to achieve glycemic targets with non-pharmacological therapy (MNT & Physical activity) within target days and if target BGs are not achieved at any point of pregnancy after 1 to 2 weeks on MNT and exercise.*
- *Recommended insulins during pregnancy are: short-acting regular insulin, NPH, Aspart, Lispro and Detemir.*
- *Glulisine, Glargine and Degludec are pregnancy category C.*
- *Mixed use of conventional insulin with analogue insulin is not recommended.*
- *Required initial insulin dose is 0.5 to 1.0 U/kg body weight. Obese may require higher dose.*
- *Glycemic targets in pregnancy are: HbA1C <6.5%, FBG ≤92 mg/dL (5.1 mmol/L), 1 hr PPG ≤140 mg/dL (7.8 mmol/L) or 2-hr PPG ≤120 mg/dL (6.7 mmol/L).*

Strict glycemic control is mandatory before and throughout pregnancy in pre-gestational diabetes and during pregnancy in GDM, as it plays a vital role in decreasing poor maternal and fetal outcomes. As the prevalence of diabetes in young is increasing, the prevalence of pre-gestational diabetes is likely to increase in the pregnant population [1]. Uncontrolled diabetes during pregnancy may complicate pre-gestational diabetes with teratogenicity and GDM by poor perinatal outcome.

1. Insulin choice in Pregnancy

1.1.: Insulin is the standard of care to attain optimal glucose control in pregnancy. Multiple methods and regimens are available to initiate insulin.

1.2.: Available insulins and associated pregnancy category are given at Table 1 [2-14].

1.2.: The choice of protocol usually is based on clinician and patient's comfort and preference.

1.3.: Pregnancy does not have sufficient time as both maternal and fetal risks increases rapidly with poor glycemic control and quick control is mandatory. Accurate and timely adjustments depend on accurate blood glucose testing, type of insulin used, and consistent diet plan.

2. Insulin dosing in Pregnancy[15]:

2.1.: Required initial insulin dose is 0.5 to 1.0 U/kg body weight/day.

2.2.: Obese women may need higher dose.

2.3.: Treatment should be individualized and graded to reach the targets.

3. Glycemic Target [15]:

3.1.: Strict glycemic control is of utmost importance in all stages of pregnancy for women diagnosed with GDM, type 1 diabetes, or type 2 diabetes.

3.2.: Glycemic targets in pregnancy are HbA1C <6.5%, FBG ≤92 mg/dL (5.1 mmol/L), 1 hr PPG ≤ 140 mg/dL (7.8 mmol/L) or 2-hr PPG ≤120 mg/dL (6.7 mmol/L). [Table 2]

4. Insulin protocol in pregnancy[15]:

4.1.: According to "GDM: SAFES Recommendations and action plan"insulin therapy should be considered if one fails to achieve glycemic targets with non-pharmacological therapy (MNT & Physical activity) within target days and if target BGs are not achieved at any point of pregnancy after 1 to 2 weeks on MNT and exercise

4.2.: During FIRST TRIMESTER and THIRD TRIMESTER [Table 3].

4.2.a.: If FPG is ≥92 mg/dl (≥5.1 mmol/L) to 109 mg/dl (6.0 mmol/L) and or 2h PPG is ≥120 mg/dl (≥6.7 mmol/L) to 139 mg/dl (7.7 mmol/L) non-pharmacological therapy is started and continued. If BG targets are not achieved within 1 week, along with non-pharmacological therapy, pharmacological treatment should be started.

4.2.b.: If FPG is ≥110 mg/dl (≥6.1 mmol/L) to 125 mg/dl (6.9 mmol/L) and or 2h PPG is ≥140 mg/dl (≥7.8 mmol/L) to 199 mg/dl (11.0 mmol/L) non-pharmacological therapy is started & continued for 3 days. If good improvement after 3 days, non-pharmacological therapy can be continued for 1 week. If BG target achieved after 1 week, then non-pharmacological therapy is continued. If BG targets are not achieved, pharmacological treatment should be started along with non-Pharmacological therapy.

4.2.c.: If FPG is ≥125 mg/dl (≥7.0 mmol/L) and or 2h PPG is ≥200 mg/dl (≥11.1mmol/L), along with non-pharmacological therapy, pharmacological therapy should be started at the onset of treatment.

4.3.: During SECOND TRIMESTER [Table 4]:

4.3.a: If FPG is ≥92 mg/dl (≥5.1 mmol/L) to 109 mg/dl (6.0 mmol/L) and or 2h PPG is ≥120 mg/dl (≥6.7 mmol/L) to 139 mg/dl (7.7 mmol/L) non-pharmacological therapy is started & continued. If BG targets are not achieved within 2 weeks for uncomplicated cases and 1 week for complicated cases

(Pre-eclampsia, polyhydramnios) pharmacological treatment should be started along with non-pharmacological therapy.

4.3.b.: If FPG is ≥110 mg/dl (≥6.1 mmol/L) to 125 mg/dl (6.9 mmol/L) and or 2h PPG is ≥140 mg/dl (≥7.8 mmol/L) to 199 mg/dl (11.0 mmol/L) non-pharmacological therapy can be started & continued for 1 week. If BG targets are achieved after 1 week, then non-pharmacological therapy is continued. If BG targets are not achieved, pharmacological treatment should be started along with non-pharmacological therapy.

4.3.c.: If FPG is ≥125 mg/dl (≥7.0 mmol/L) and or 2h PPG is ≥200 mg/dl (≥11.1mmol/L), along with non-pharmacological therapy, pharmacological therapy should be started at the onset of treatment.

5. Insulin therapy in diabetes with pregnancy (pre-gestational diabetes)

5.1.: Preconception care is important for all women with preexisting type 1 or type 2 diabetes. Education regarding strategies to maintain adequate nutrition and glucose control before conception, during pregnancy and in the postpartum period is cornerstone of good pregnancy outcome.

5.2.: When women with diabetes attains glycemic control (HbA1c<6.5%) before pregnancy then she will plan for conception and this glycemic target must be achieved by insulin treatment. In that case OAD should be shifted to pregnancy safe insulin at least 3 months before planning for conception [15].

6. Premixed insulin is not a good choice of insulin during pregnancy and be considered on individual basis where patients are unwilling to or unable to take basal bolus or split mix regimen [15.]

7. Mixed use of conventional insulin with analogue insulin is not recommended [15].

Table 1: Summary of Available Insulin and Associated Pregnancy Category [2-14].

Insulin	Pregnancy category
Regular 40U/100U	B
Aspart/Lispro	B
Glulisine	C
NPH	B
Detemir	B
Glargine	C
Degludec	C

Table 2: Glycemic targets in pregnancy	mg/dl	mmol/L
FPG	<92	<5.1
1 h PPG	< 140	< 7.8
2 h PPG	< 120	< 6.7
N.B.: Adopted from GDM: SAFES Recommendations and action plan, Dhaka, SAFES, 2017 [15].		

Table 3: TREATMENT IN 1st and 3rd TRIMESTER[15]						
GDM PLASMA GLUCOSE TARGETS AND TREATMENT PROTOCOL						
FIRST TRIMESTER:						
	PG values			**Treatment at onset**	**Change of treatment if target not achieved within**	**Treatment reviewed & continued**
FPG	≥92 mg/dl (≥5.1 mmol/L)	To	109 mg/dl (6.0 mmol/L)	NPT	1 week	NPT+PT
and/or						
2h PPG	≥120 mg/dl (≥6.7 mmol/L)	To	139 mg/dl (7.7 mmol/L)	NPT	1 week	NPT+PT
FPG	≥110 mg/dl (≥6.1 mmol/L)	To	125 mg/dl (6.9 mmol/L)	NPT	3 days	NPT+PT
and/or						
2h PPG	≥140 mg/dl (≥7.8 mmol/L)	To	199 mg/dl (11.0 mmol/L)	NPT	3 days	NPT+PT
FPG	≥125 mg/dl (≥7.0 mmol/L)			NPT+PT x		NPT+PT
and/or						
2h PPG	≥200 mg/dl (≥11.1mmol/L)			NPT+PT x		NPT+PT
NPT: Non-pharmacological treatment, PT: Pharmacological treatment						

Table 4: TREATMENT IN 2nd TRIMESTER[15]						
GDM PLASMA GLUCOSE TARGETS AND TREATMENT PROTOCOL						
SECOND TRIMESTER:						
	PG values			**Treatment at onset**	**Change of treatment if target not achieved within**	**Treatment reviewed & continued**
FPG	≥92 mg/dl (≥5.1 mmol/L)	To	109 mg/dl (6.0 mmol/L)	NPT	2 week/1 week Uncomplicated /complicated	NPT+PT
and/or						
2h PPG	**≥120 mg/dl (≥6.7 mmol/L)**	To	139 mg/dl (7.7 mmol/L)	NPT	2 week/1 week Uncomplicated /complicated	NPT+PT
FPG	**≥110 mg/dl (≥6.1 mmol/L)**	To	125 mg/dl (6.9 mmol/L)	NPT	1 week	NPT+PT
and/or						
2h PPG	**≥140 mg/dl (≥7.8 mmol/L)**	To	199 mg/dl (11.0 mmol/L)	NPT	1 week	NPT+PT
FPG	≥125 mg/dl (≥7.0 mmol/L)			NPT+PT	X	NPT+PT
and/or						
2h PPG	≥200 mg/dl (≥11.1mmol/L)			NPT+PT	X	NPT+PT
NPT: Non-pharmacological treatment, PT: Pharmacological treatment						

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15. *GDM: SAFES Recommendations and action plan, Dhaka, SAFES, 2017.*

Section 8:

Insulin in Chronic Kidney Disease (CKD):

Key Points:

- *In CKD, there is increased risk of hypoglycemia while using insulin due to decreased clearance.*
- *All available insulin preparations can be used in patients with CKD.*
- *Usually no dose adjustment is required for total daily dose (TDD) of insulin if the eGFR is >50 mL/min.*
- *Reduction to 75% of TDD of insulin when the eGFR is between 10 and 50 mL/min and to 50% of TDD for eGFR of <10 mL/min may be considered which is independent of the type of insulin being used.*
- *Long acting insulin/ basal insulin analogue should be used with reduced dose during initiation and intensification.*

As kidney disease progresses there is increased risk of hypoglycemia due to decreased clearance of insulin. The kidney is responsible for about 30 to 80 % of insulin removal; reduced kidney function is associated with a prolonged insulin half-life and a decrease in insulin requirements as GFR declines. All available insulin preparations can be used in patients with CKD. The insulin type, dose and administration must be tailored to each patient to achieve goal glycemic while limiting the risk of hypoglycemia. Usually no dose adjustment is required for total daily dose (TDD) of insulin if the eGFR is >50 mL/min. Nevertheless, reduction to 75% of TDD when the eGFR is between 10 and 50 mL/min and to 50% of TDD for eGFR of <10 mL/min may be considered which is independent of the type of insulin being used. With reduced eGFR, lower dose of long acting insulin/ basal insulin analogue should be used during initiation and intensification. Any regimen, e.g.; premixed or basal bolus may be used. Close monitoring of blood glucose and adjustment of insulin doses are required to avoid hypoglycemia [1].

Reference:

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Section 9:

Insulin in Chronic Liver Disease (CLD):

Key Points:

- *In CLD, Insulin therapy is considered as the safest and most effective therapy.*
- *In patients with DM and chronic liver disease, there is increase chance of post-prandial hyperglycemia and fasting hypoglycemia.*
- *Short-acting insulins are preferred.*
- *Insulin analogs may offer improved glycemic control compared to standard insulin with a lower risk for nocturnal and severe hypoglycemia.*
- *In CLD, short acting insulin analogues can be used just after meal if patient have nausea or reduced appetite.*

Insulin therapy is considered as the safest and most effective therapy in patients with liver dysfunction, with the limitation of increased risk of hypoglycemia. Short-acting insulin are preferred because the duration of action may vary in such situations. In patients with DM and chronic liver disease, there is increase chance of post-prandial hyperglycemia and fasting hypoglycemia. Without increasing costs, insulin analogs may offer equivalent or improved glycemic control compared to standard insulin while being associated with a lower risk for hypoglycemia, particularly nocturnal and severe hypoglycemia.The pharmacokinetics and pharmacodynamics of rapid-acting insulin analogs suggest that they can be given just after meals. This is of benefit to many patients with advanced CLD as they may have nausea and reduced appetite and hence have the option of using rapid-acting insulin analogs just after their meals depending on their intake [1].

Frequent dose adjustment and careful glucose monitoring for DM with CLD patients is thus very important to minimize the risk of hypoglycemia or hyperglycemia. Meals should be taken every three-hourly to avoid hypoglycemia.

Reference:

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Section 10:

Barriers to Insulin Initiation:

Common barriers to insulin initiation and strategies to overcome them.

Patient identified barrier	Strategies to address barrier
Fear of injection pain [1,2,3]	Demonstrate available tools and needle sizes [2]. Provide adequate practice and support of injections to overcome fear [3].
Fear of weight gain [1,2]	Dietary control and adequate exercise can minimize weight gain while also improving glycaemic control [3].
Inability to manage insulin regimen [1].	Provide education and support. Simplification of regimen and use of simple self-titration tools [1].
Hypoglycemia [1,2].	Use of short acting analogues, pre-mixed analogues, long-acting analogues to reduce hypoglycemia risk. Provide education on recognition, management and avoidance of hypoglycemia. Reassure that incidence of serious hypoglycemia is rare [1].
Fear that diabetes has worsend or has become 'end stage' [1,2,3].	Introduce insulin as a diabetes management tool early in course of T2DM (24, 25). Reassure that insulin requirement is an inevitable part of the disease course [1].
Decreased lifestyle flexibility [1,2].	Explain different insulin regimens and injection schedules [1].
Social stigma associated with injecting [1,2,3].	Introduce tools such as insulin pens to make injecting simpler [1].
Insulin is not beneficial or can harm health [1,2,4].	Provide adequate education.

References:

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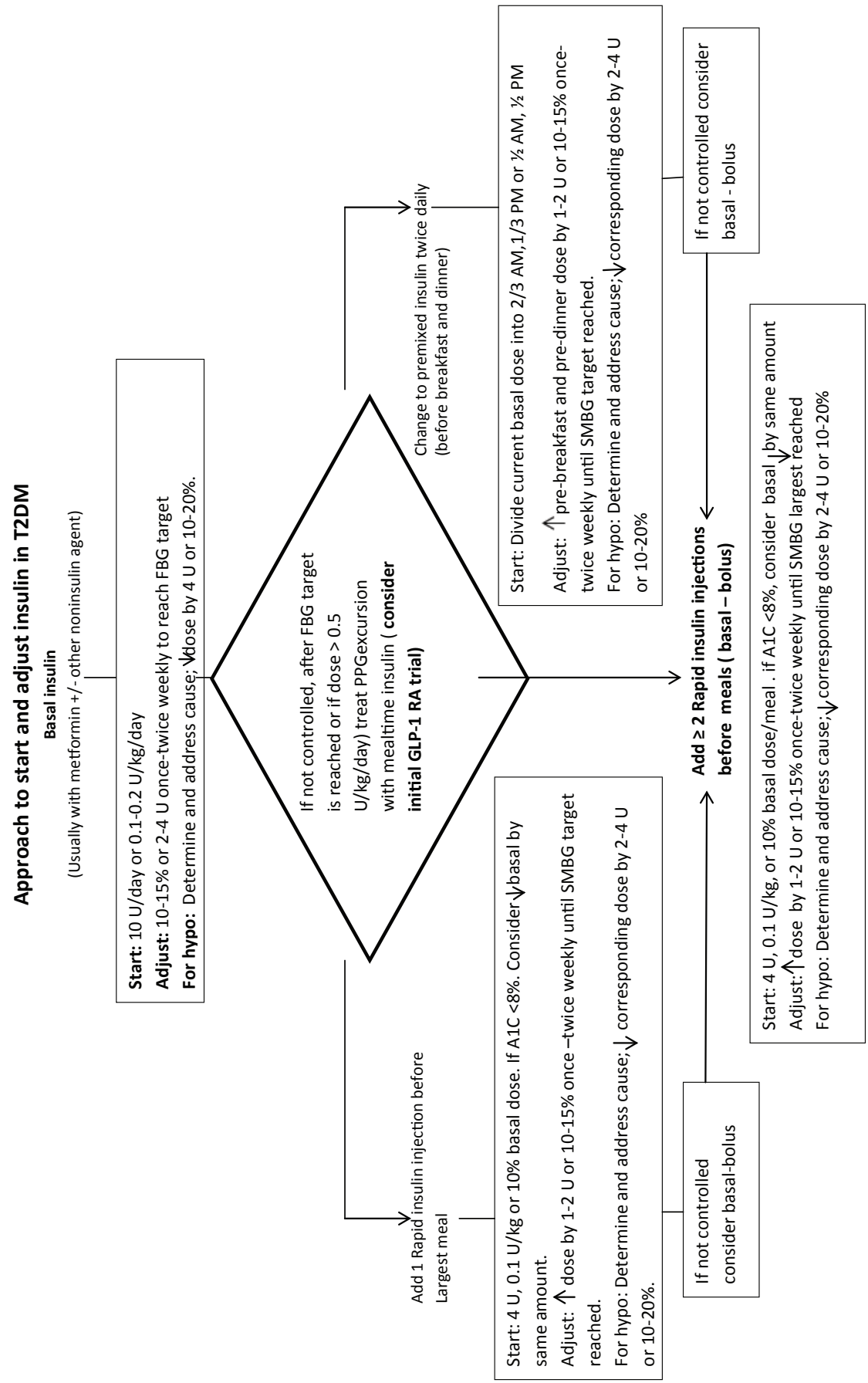
Approach to start and adjust insulin in T2DM
Basal insulin
(Usually with metformin +/- other noninsulin agent)
Start: 10 U/day or 0.1-0.2 U/kg/day
Adjust: 10-15% or 2-4 U once-twice weekly to reach FBG target
For hypo: Determine and address cause; dose by 4 U or 10-20%.
If not controlled, after FBG target is reached or if dose > 0.5 U/kg/day) treat PPGexcursion with mealtime insulin (consider initial GLP-1 RA trial)
Change to premixed insulin twice daily (before breakfast and dinner)
Start: Divide current basal dose into 2/3 AM,1/3 PM or ½ AM, ½ PM
Adjust: pre-breakfast and pre-dinner dose by 1-2 U or 10-15% once-twice weekly until SMBG target reached.
For hypo: Determine and address cause; corresponding dose by 2-4 U or 10-20%
If not controlled consider basal - bolus
Add ≥ 2 Rapid insulin injections before meals (basal – bolus)
Add 1 Rapid insulin injection before Largest meal
Start: 4 U, 0.1 U/kg or 10% basal dose. If A1C <8%. Consider basal by same amount.
Adjust: dose by 1-2 U or 10-15% once –twice weekly until SMBG target reached.
For hypo: Determine and address cause; corresponding dose by 2-4 U or 10-20%.
If not controlled consider basal-bolus
Start: 4 U, 0.1 U/kg, or 10% basal dose/meal . if A1C <8%, consider basal by same amount
Adjust: dose by 1-2 U or 10-15% once-twice weekly until SMBG largest reached
For hypo: Determine and address cause; corresponding dose by 2-4 U or 10-20%

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