• INSULIN BASED TREATMENT

• INITIATION, TITRATION and MAINTENANCE

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Diabetes global problems

India Currently 58 Million People
Future Estimation 80 Million in 2030
More than 371 Millions people have diabetes globally

Half of people with diabetes are undiagnosed
48 Million people die due to diabetes every year
Globaly Expected to increase to 438 Millions by year 2030
Estimated every 30 sec one leg lost due to diabetes
Insulin Based Treatment Need Revised
Food Plan Exercise Programme

Synchronized to Insulin Actions
Initiation of Insulin

In T2DM
Initiated in two ways

1. Significant hyperglycemia
   HbA1c >11% at diagnosis

2. Non-insulin therapies failing to achieve target HbA1c
Beta Cell

Chronic hyperglycemia

Glucotoxicity

Decrease in beta-cell mass owing to hyperglycemia, accelerated beta cell apoptosis

Precursor to glucotoxicity

Beta cell exhaustion is reversible
Cascade of Events

- Hyperglycemia to beta cell exhaustion is exacerbated by hyperstimulation of pancreatic beta cell

- Direct consequence of hyperglycemia
Beta Cell Exhaustion - treated with intermittent episode of insulin therapy

- Beta cell rest while glucotoxicity subsides
- Consequently euglycemia is reached
- Insulin may be discontinued

With factual glucotoxicity, it is likely that the patient always require exogenous insulin to maintain glycemic control
Preparation for Insulin Initiation

Identify underlying defect before initiation of insulin

First, 3 conditions to consider

1. Fasting hyperglycemia
2. Postprandial hyperglycemia
3. Overall metabolic derangement ideally

HbA1c & C-Peptide measurement to identify the defect

SMBG or CGM
Preparing the Patient

Often prolonged as much as 8 year from diagnosis.

Advancement from MNT to oral monotherapy to combination therapy and finally to insulin therapy.

Clinical inertia
Patients Worried in Starting Insulin Therapy

- Fear of injection
- Risk of hypoglycemia
- Concern for potential weight gain
- Self blame (flame to making DM) &
- Belief that insulin would not be effective in controlling DM
### CME for Primary Care Provider

* Focusing on the use of insulin in T2 DM
* Tool to address patient barrier to insulin
* Approach
  - Starting insulin earlier in the natural history of diabetes
  - At a lower HbA1c
Traditionally, insulin syringe & vial. Syringe & needle technically improved

1980 – Insulin pens were introduced
Pen Device Contains

- Dial for selection of dosing
- Removable needle for adjustment
- Reservoir for insulin
Reusable Pen Requires Replacement of Insulin Cartridges

- Prefilled discarded insulin pens
- Pen needle in a variety of length
  - 4, 5, 6, 8 or 12 mm
- Thickness
  - 29, 30 or 31 gauge
- Audible click
- Priming step
  - 1 or 2 units of insulin
- Hold the needle for 5 seconds to assure insulin delivery
Step 2: Selecting the Insulin Therapy

- 2/3rd of individuals with T2 DM
  - Managed upto 10 years using standard method
- Asian descent may develop relative insulin deficiency earlier than Caucasians
- 3 avenues lead to insulin initiation
  1. Severe acute hyperglycemia HbA1c >11%
  2. Chronic hyperglycemia &
  3. Failure of non-insulin therapy to restore glucose homostasis
Insulin Initiation

- Initiation of insulin is different on these three instances
- Metformin combined with sulfonylurea
  - Fails to restore or maintain glucose level – consistent with normal carbohydrate metabolism, insulin therapy is employed specifically to replace the action of the secretogogues
- Under these circumstances, it is important to supplement the insulin production
- Failure of sulphonylurea is usually manifest in both post prandial and between meals hyperglycemia
  - An alternative scenario beginning more common is failure of 3 non-insulin agents
Choice of Insulin Regimen

• 3 primary insulin regimens
  1. Background (Basal) insulin with oral agents
  2. Mixed insulin (with or without a sensitizer)
  3. Background (Basal) & meal time bolus insulin
• The choice of the insulin regimen is based on a number of factors
  – Eg. Fasting hyperglycemia
    – Introduction of basal insulin along with oral agent may prove real or retrieve hypoglycemic reactions that could forestall improvement in glycemic control
• Pattern of hyperglycemia
  – Fasting, pre and post meal – mixed or basal/insulin regimen
• Patients LSM important consideration in the choice of insulin regimen
Basal Insulin Options

• 1. long acting insulin analogue (Glargine or Detimer/NPH) once daily usually at bed time

Initiate basal insulin at low dose to

• 1. Improve overall basal insulin level
• 2. Improve fasting hyperglycemia
• It is important to determine, medications are no longer effective (non-insulin agents)
• 2 principle agent, sulphonylureas & metformin
  – Considered to be lacking in optional efficiency at 75% of maximum dose
    • No longer able to resume post-meal and overnight hyperglycemia
• Under these circumstances, add background basal insulin & maintain the oral therapy or GLP-1 agonist
• 3 approaches to use basal insulin when non-insulin agents fail
  – Background (Basal) insulin initiation prior to the morning meal
  – Background insulin (Basal) prior to bed time
  – Split background (Basal) insulin between morning & bedtime
Each approach has clinical indicators

- Example

FGL is below 80mg/dl

Morning PPG is above 180mg/dl

Then morning long acting insulin is initiated

- If FBG is above 110mg/dl &
- PPG is around 180mg/dl, then evening at bedtime insulin is initiated
- If both FPG/PPG levels exceed targets, the split basal insulin is initiate

(This approach significantly lessens the risk of hypoglycemia)
Starting Background (Basal) Insulin Therapies with Non-Insulin Agents

Starting dose of Basal insulin based on 2 factors

HbA1c & Weight
• **HbA1c at or above 9%,** the Basal Insulin (BI) dose is calculated at 0.2 U/kg

• **If HbA1c is below 9%,** the starting dose is 0.1 IU/kg/OD at bed time

• **Patients with newly diagnosed DM and HbA1c is above 11%**
  - Starting combination oral therapy
    • Metformin or Sulphonyl urea

• **With background insulin at 0.2IU/kg OD is recommended**

• **Oral agents, particularly secretagogues and/or sensitizers**
  - Usually continued with the addition of BI to maintain their effect on PPG
• Amount of insulin can be increased by 1-5 units every 3-7 days based on the fasting SMBG or overnight CGM
  – Until glucose improves to within targets (at total daily dose of 0.5-1.2 IU/kg is reached)

• Same principle can be used to NPH

• However, since this type of insulin has a peak action between 8 to 10 hours, it is vital that SMBG can be done at ascertain the glucose values at the peak action time of NPH & avoid *nocturnal hypoglycemia*

• If the SMBG pattern show elevated glucose levels in the day
  – Changing the administration of long acting insulin from bed time to morning may be warranted

• Also, as insulin dose increases, dividing the dose of long acting insulin between morning & evening may also be done
Adding Mealtime (Bolus) Insulin Therapy

• Whether NPH or long acting insulin, used after reaching a total daily dose of 0.5 - 0.7 IU/kg, rapid acting insulin needs to be incrementally added to the regimen
  – Often called basal plan insulin therapy

• Select the period with the highest post meal glucose
  – Usually between the meals of the day, constituting the highest carbohydrate content

• Maintain the DPP4 inhibitor or GLP-1 agonist if there is a positive response

• Stop sulphonylurea & maintain or initiate metformin

• Start rapid acting insulin 0.1IU/kg
  – Before 15 minutes the selected meal

• In order to reduce risk hypoglycemia
  – Subtract 0.1IU/kg from the background or basal insulin
Adding Mealtime (Bolus) Insulin Therapy

- Strategy continues with the same total daily dose of insulin (0.1IU/kg basal + 0.1IU/kg bolus)
  - Gradually changes the proportion of basal to bolus insulin to more physiological ratio
- Slow titrations of the rapid-acting insulin & careful monitoring
  - Should prevent hypoglycemia
- Key to initiation of insulin is not to add calories, but to redistribute the current calorie intake so that times at risk of hypoglycemia are addressed
- Often, redistribution of 10% of mealtime calories between meal times is sufficient
Adding Mealtime (Bolus) Insulin Therapy

- If blood glucose targets are not achieved with the addition of one injection of rapid-acting insulin, additional injection can be added based on the glucose pattern
  - Same principle applies 0.1IU/kg of rapid acting insulin prior to the selected meal is added until currently reducing the basal insulin dose by 0.1 IU/kg
- When the 2nd injection of rapid acting insulin is started, stop the secretagogues
- Insulin sensitizers are usually continued if there is evidence of effectiveness
- Transition approach allows for a gradual introduction of physiological insulin therapy or basal/bolus insulin therapy
Premixed Insulin Therapy

- Used of premixed insulin as a fixed combination of either

  1. NPH/regular or analogues with rapid acting component and intermediate action component is frequently used in primary care setting
     - This insulin regimen employs two injections of premixed insulin
       - One injection before the morning meal & one injection before the evening meal
     - Major advantage convenience of two injections/day
     - It should be able to maintain normal insulin secretion pattern
     - Premixed insulin is available in various ratio of intermediate action & short or rapid acting insulin, 75/25, 70/30 & 50/50
Premixed Insulin Therapy

- Requires constant meal & snacks time
- Frequent SMBG to reduce the risk of hypoglycemia
- With premixed insulin, any change required in the intermediate acting insulin dose also changes the short acting or rapid acting insulin dose
- Mixed or delayed meals or snacks can be probably made with this regimen owing to the risk of hypoglycemia
Starting Premixed Insulin Therapy

- Starting dose of premixed insulin
  - Calculate based on current HbA₁c & weight. When using premixed insulin, secretagogues should be discontinued, GLP₁ agonist, DPP₄ inhibitors & insulin sensitizers are carefully monitored.
  - Effectiveness of these medications should be reconsidered in the light of the action of the premixed insulin.

- If the HbA₁c is 9% or above, the starting dose premixed insulin calculated at 0.2IU/kg before the morning & evening meals.
  - Total daily dose of 0.4IU/kg.

- If HbA₁c is 9%, the starting dose is calculated at 0.1IU/kg before the morning & evening meals.
  - Total daily dose 0.2IU/kg.
Starting Premixed Insulin Therapy (Contd...)

- A pattern of low or high blood glucose levels before the evening meals requires adjustment of the morning premixed insulin dose

- Hypoglycemia must be corrected first by decreased the insulin responsible by 1-3 units

- Further insulin decreases are made, if SMBG continues <70mg/dl

- Insulin adjustments can be made by the patient based on SMBG data one or more times/week

- If a persistent pattern of hypoglycemia or hyperglycemia cannot be corrected by adjustment of the premixed insulin, advancing to basal/bolus insulin regimen is recommended
Advancing from Premixed to Basal/Bolus Insulin Therapy

1. If glycemic targets are not reached with adjusting premixed insulin

2. Pattern of hypo or hyperglycemia remains despite maximum insulin therapy

3. If the total daily insulin dose is greater than 1.5IU/kg, it is basal/bolus insulin regimen
   - Transition is made by determining the total daily dose of insulin
Advancing from Premixed to Basal/Bolus Insulin Therapy (Contd..)

- If the current HbA1c is below 9%, reduce the total daily insulin dose by 10%
- If HbA1c is 9 or above, maintain the current total daily insulin dose
- Decide the total daily dose into 50% of long acting background/basal insulin at bed time and the remaining 50% as rapid acting insulin divided evenly between 3 meals
- Adjustment can be made later based on the individual's meal plan
Advancing from Premixed to Basal/Bolus Insulin Therapy (Contd..)

- **Example**
  - If a target carbohydrate meal is eaten in the evening, more rapid acting insulin can be given prior to that meal.
  - For patients with HbA1c 8.4% & current total daily premixed insulin dose of 60 units (0.8IU/kg)
    - First step would be to decrease the total daily insulin dose by 10% or 54 units – 50% will be delivered as peak round insulin
      - 27 U long acting insulin at bed time
      - 50% divided between meals
        » 9 U of rapid acting insulin within 15 minutes before each meal.
Background (Basal) & Mealtime (Bolus) Insulin Therapy

• Basal/bolus insulin regimen is the most physiological insulin regimen available today
• It provides a long acting or basal insulin and supplemental rapid-acting insulin
• It requires upto 4 or more injections daily
Basal bolus insulin therapy is initiated at diagnosis

- HbA1c is above 11% for existing diabetes
- It is started where combination during therapy is no longer effective
- If using a secretogogue immediately stop
- If GLP-1 agonists, DPP-inhibitors or insulin sensitizers are used, carefully blood glucose levels in combination with low-dose insulin, hypoglycemia may occur
- If HbA1c is 9% or above, basal insulin warrants a long acting insulin (Glargine/Detimer) is started at 0.2U/kg
  - Background insulin can be given any time
Background (Basal) & Mealtime (Bolus) Insulin Therapy - START

- Mealtime (bolus) insulin is calculated at 0.2U/kg with dose divided between meals
  - The result will be total daily dose of 0.4/kg (50% basal % 50% bolus)
- However for HbA1c <9% the safest starting dose is 0.1U/kg of long acting insulin (Glargine or detemir) at bed time & 0.1U/kg of rapid acting or regular insulin divided between meals
  - The result is total daily dose of 0.2 U/kg divided at 50% long acting insulin, 50% rapid acting insulin
If NPH is used as basal insulin, the regimen is more complex.

Morning NPH should peak in time to dampen the glucose excursion following the mid-day meal, and the evening NPH should reduce the glucose excursion caused by the evening meal &/or hepatic glucose output.

Start NPH at 0.1U/kg at bed time & split into two injections if needed.
Prior to initiation of short acting insulin, monitor glucose levels before the mid-day meal & 1 & 2 hours afterward.

This should provide sufficient information regarding typical PPG excursion.

Add 0.05 U/kg short acting insulin before the mid-day meal.

Continue monitor to detect hypoglycemia.

Continue to increase the dose by 10% every 3 days until glucose levels before dinner between 70- & 140mg/dl.

Do not exceed 0.2U/kg of short acting insulin with the mid-day meal.

If this level is not reached, add short acting insulin 0.05U/kg before the breakfast.
Background (Basal)/Meal Time (Bolus) Insulin Therapy Adjustment

- It follows the same principle with basal and premixed insulin
- If a pattern of hypoglycemia presents this should be targeted first by decreasing the insulin responsible by 1-3 units
- Hypoglycemia overnight or prior to the morning meal require adjustment of the long-acting insulin
- Hypoglycemia prior to a meal requires decreasing the insulin responsible
  - Eg. a pattern of low blood glucose (<70mg/dl) prior to mid-day meal necessitating decreasing the AM rapid acting insulin
• **Education on hypoglycemia and its identification**
  – Very important

• **Most of T2 DM patients after 10 years**
  – Requires insulin

• **Early aggressive insulin therapy**
  – Very important to prevent beta cell apoptosis
-- Start insulin early in T2DM
-- Criteria to start insulin depend on weight and A1C
-- Situation like DKA, Surgery, GDM etc require Special Consideration
-- Doctor must be well versed with Insulin devices
-- Education of patient regarding Hypoglycemia SMBG is more important.
THANKYOU