Section: Endocrinology

Review Article

THE DISCOVERY OF INSULIN AND ITS CURRENT EVOLUTION

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ABSTRACT

The discovery of Insulin & its current evolution has completely transformed the lives of millions of diabetic people. In the pre-insulin era, diagnosis of T1DM was almost death sentence for them. Eventually as the time passed, a variety of insulin were developed and these revolutionized the treatment of diabetes. Insulin continues to be the cornerstone of diabetes management. Insulin analogs have made insulin injection more convenient and more closely mimicking insulin physiology with further minimization of hypoglycaemia risk.

Keywords: DISCOVERY, INSULIN.

INTRODUCTION

The discovery of Insulin & its current evolution has completely transformed the lives of millions of diabetic people in a meaningful manner. In the pre-insulin era, diagnosis of T1DM was almost death sentence for them. There was not much that doctors could do to manage these patients except for very low calorie diet. The year 1921, turned out to be a great milestone in the history of diabetes when Banting & Best discovered Insulin. Insulin first time made available for human use since year 1923. Eventually, as the time passed, a variety of insulin preparations were developed by various manufacturers. Initially, bovine/ porcine insulin were available but these had allergic reactions in many patients and were immunogenic as well.[1] So a need was felt for developing newer insulins. Then Hagedon discovered that addition of protamine resulted more stable & longer acting insulin.[2] This preparation was called NPH insulin, addition of Zn to insulin was another technique to prolong action of insulin.[3] Now a days most of the insulins are made by Genetic engineering DNA recombinant technology, called Bio insulins. These are devoid of allergic reactions & less immunogenic. [4]

Basic variants of human insulins are – Regular insulin, NPH insulin, Mixture of regular and NPH insulin in variety of combinations like premix insulin (30: 70 , 50:50, 25:75). These preparations have certain limitations. We will discuss on this in later part of this article. Further there was a need for shorter & quicker acting insulin mimicking the rapid physiological insulin secretion following meal and this insulin should be quickly, degraded & removed from the system, so there will not be any inter meal hypoglycemia. There was also a need for longer acting insulin that shouldn't have any peak & will provide 24 hrs basal insulin support mimicking physiological low rate of insulin secretion between meals & overnight. We need a combination of ideal short and ideal long acting insulin analogs for severely insulinopenic patients. One co formulation insulin preparation is now available that has closely met this need.

Indications of Insulin Use

Insulin continues to be gold standard treatment option for any type of diabetes mellitus patient. Till date no other anti-diabetic agents can reduce HbA1c as much as it does to the tune of 2%. However, if baseline HbA1c is more, you can expect much higher HbA1c reduction.[5] Insulin is the only treatment option for type 1 diabetes patients & type 2 patients need insulin in advance stages of the disease & in certain other circumstances they may need insulin therapy for short duration like during active infection, perioperative period, during acute metabolic complications like DKA, HHS, during pregnancy, when developed hepatic / renal impairments, when having severe osmotic symptoms and in catabolic phase of the disease.[6] T2DM patients also need insulin if baseline entry level HbA1c > 9% or Fasting Glucose > 300 mg/dl.[6] After reduction of glycaemia when glucolipotoxicity is improved these patients

again can be managed by OADs. When three oral antidiabetic drugs (OAD) fail to achieve desired glycemic goals in T2 DM patients, they need insulin therapy. Despite enormous development of OADs with extra glycemic benefits of OADS, Insulin continues to be cornerstone therapy of diabetes mellitus irrespective of type of diabetes. It does not need any cardiovascular outcome trial to establish its safety in diabetic patients.

Older and Newer Insulins

Insulin analogs are boon for diabetes patients and more closely mimicking physiological insulin like action profile.[7] Advantages of insulin analogs are - early onset of action, shorter duration of action so less hypoglycemia risk, meal time flexibility, can be administered within 15 minutes after starting of meals, more predictable absorption from s/c injection site so uniform glucose lowering action less glycemic variability, more time in range(TIR) & less intra individual & inter individual variability in response.[8]

NPH insulin has certain disadvantages like it does not provide 24hrs basal insulin coverage, it has a peak, so more chance of hypoglycemic spell, duration of action is ~ 15 hrs, so needs to be given twice daily injection and marked intra individual & inter individual variability in responses.[9]

Premix insulin contains regular insulin (short acting) and Intermediate acting NPH insulin. It usually needs to be given twice daily, down or up titration of individual insulin component of premix regimen according to self-monitoring of blood glucose (SMBG) report is difficult. As these two components have different solubility, on keeping they separate with each other. So needs to be suspension & resuspension before injecting / drawing insulin into syringe.[10] Otherwise desired proportion of different components will not be drawn in syringe. Sometimes, shouldering effects may occur. It refers to the prolonged and potentially unwanted glucose lowering action of short acting component of premix regimen due to protamination of short acting insulin component so creating a shoulder on the insulin action curve.[11]

Co-formulation of Ideg-Asp advantages are superior control of FPG, 2 hrs pp, & thus HbA1c.It will have lower mean total daily insulin requirement, so less painful prick, lesser glycemic variability as two component remain in the solution, fewer confirmed nocturnal hypoglycemia, severe hypoglycemic events requiring hospital admission. One prick/ two pricks in a day control 24 hrs hyperglycemia and flexibility in dose timing.[12]

FiAsp is faster acting insulin aspart, it allows more flexibility in injection timings. It contains l-arginine and nicotinamide as excipients that allows faster absorption from injection site.[13] Its action starts within 2 minutes after injection.[13] This property particularly helpful for kids who do not want to wait for food. Sometimes children take erratic amount of food, in that case FiAsp preparation allows prandial insulin dose adjustment according to amount of food ingested. This is also helpful for sick patients whose food intake is often unpredictable. This is in contrast to usual regular insulin which needs 30 mins to start in action, so patient has to wait during this time and thereafter they can start taking food. This is to match the action profile of regular insulin. This is very troublesome for working class of people. Long action analogs are devoid of peak & provides smooth 24hrs basal insulin support.[14] The most widely used preparation is Insulin glargine U100. Recently Insulin glargine 300, Insulin degludac are available. These are superior option than glargine U100. Disadvantages of glargine U 100 insulin-------Its duration of action is between 18-20 hrs. So in next 4-6 hrs, it is unable to provide basal insulin support.[15] For this reason sometimes we have to give glargine twice daily. It's action is not entirely peakless, when it has to be given more than 30 units in a day, it has some peak thus can cause hypoglycaemia.[15] As after subcutaneous injection it gets precipitated and form micro precipitate and subsequent dissolution from micro precipitate is not uniform so variation in absorption of glargine into blood stream happens. So it's glucose lowering efficacy is not uniform throughout the day.[16] In contrast, Insulin degludac is ultra-long acting basal insulin analog.It has a terminal half-life of 25 hrs,twice of glargine insulin and duration of action is 42 hrs.[17] It does not have any peak & uniform glucose lowering in a day so less day to day and intraday variation in required degludac doses.[17] It allows broader dosing window with minimum 8 hrs and maximum 40 hrs gap between two subsequent daily doses are possible without compromising glucose lowering ability and on the other hand risk of hypoglycaemia.[18] This is important because such an option would positively impact patients abilities to lead modern hectic lives including travel, dining out,changing bed times etc.

Insulin therapy has three components---- insulin initiation, titration and intensification.

Different insulin regimens

1. Basal Insulin only ---- FPG mainly depends upon nocturnal hepatic glucose production.[19] We need to fix fasting sugar first, as it has been seen at higher HbA1c, contribution of FPG is maximum that is if someone has high FPG, means higher baseline at the beginning of the day, and as the day progresses with intake of each meal PPG excursion will be more.[20] Hence in this regimen single inj of long acting basal insulin at night/ any fixed time of the day is given in addition to daytime OAD.

2. Basal plus --- It comprises of addition of prandial short acting insulin before the largest meal of the day that has shown the highest glycemic excursion with nighttime basal insulin injection. The subsequent prandial insulin dose titration will be based upon post meal glucose values. People who take one large meal in a day is suitable candidate for this kind of regimen.

3. Basal bolus --- This regimen comprises of one nighttime basal insulin dose & 2-3 times prandial short acting insulin doses before each large meal. It is almost for all type 1 diabetes patients, patients with

advanced stages of T2DM patients who are severely insulin deficient and fibro calcific pancreatic diabetes (FCPD) patients.[21]

4. Insulin infusion- Insulin infusion is given during diabetic ketoacidosis (DKA), hyperglycemic hyperosmolar state (HHS).[22]

Challenges in Insulin therapy

Patients in India consider insulin prescription as a final & last stage of the disease. They sometimes feel doctors are giving them punishment as they were unable to control their blood glucose levels. So here lies the importance of counselling & diabetes educator. There is also inertia on treating doctors' side. Physicians are often reluctant in starting insulin in timely fashion. While we are treating type 2 diabetic patients, what we do generally that we start one drug after lifestyle measures failed then as the glucose control fails over the time course, we increase the dose of that particular drug, then add a second drug, then a third and the fourth drug. This kind of approach is called "treat- to- failure" approach.[23] This is discouraged now a days because this will have poor metabolic legacy and will negatively impact diabetes treatment outcome.[23] So we should start insulin in appropriate manner in all diabetic patients. Those patients in whom insulin has been prescribed, they must be educated about insulin method of administration, titration of insulin dose, how to store it, important & regular SMBG & sick day rules.

Hypoglycemia Risk & Its impact

Despite considerable advancement in diabetes management including insulin analog, Hypoglycemia remains an inevitable risk in diabetic patients regardless of insulin use. Hypoglycemia is a major barrier in maintaining satisfactory glycemic control in diabetic patients.[24] Hypoglycemia is associated with significant cardiovascular effects in vulnerable patients. These include myocardial ischemia, abnormal cardiac repolarization leading to fatal arrhythmias.[25] An association has been suggested between hypoglycemia and unexpected nocturnal death of patients with T1 DM without cardiovascular risk factors, described as "dead in bed syndrome".[26] Hypoglycemic episodes in elderly people, who often have hypoglycemic unawareness due to autonomic neuropathy and hypoglycemia associated autonomic failure (HAAF) is also dangerous.[27] One episode of hypoglycemic scares the diabetic pt. & pt. often reduce insulin dose without consulting doctor & ultimately land up into poor glycaemia. One hypoglycemic event induces massive sympathetic overdrive as a result patient will have higher risk of cardiovascular events in next few months.[28]

CONCLUSION

So, we have to choose appropriate insulin preparation & regimen according to type of diabetes, stage of the disease, presence of comorbidities, patient's lifestyle, meal pattern, patient's affordability and simultaneously minimizing the risk of developing of overall hypoglycaemia and nocturnal hypoglycaemia. All patients in whom insulin has been advised must be educated about insulin storage, proper injection techniques, insulin dose titration ad importance of SMBG at home and hypoglycaemia warnings.

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