INSULIN GUIDELINES: TAKING IT FORWARD

ABSTRACT

Majority of type 2 diabetic subjects require insulin administration at some stage in their natural history of diabetes. Notwithstanding the virtuosity of insulin in achieving glycemic control, every aspect of insulin therapy is unfortunately beset with huge differences in opinion. Furthermore as 70-80% of diabetic subjects are treated by primary care physicians, guidelines need to be simple, effective and feasible to be administered in the primary care setting without availability of dedicated diabetes care team.

Several guidelines are available for insulin initiation and intensification. However, glycemic targets remain elusive in almost 50% of subjects even in countries practicing these guidelines effectively. A plausible explanation for this failure could be the inadequacy in the guidelines or the difficult logistics involved in their implementation.

Indications for initiating insulin therapy are generally agreed upon in most of the guidelines. However, regional differences guide the choice of insulin for initiation as well as intensification. While basal insulin analogues are mostly used for initiation in Europe, USA and some parts of Asia, Premixed insulins are preferred in Asia and few European countries. Similarly intensification from basal insulin is usually done by either twice daily basal insulins or switching over to more complex basal bolus therapy. In many parts of the world intensification is done by increasing the number of pre mixed insulin injections from 1-2-3 injections a day.

Basal bolus therapy remains the gold standard insulin regimen. Unfortunately the complexities involved with the regimen, need for frequent home blood glucose monitoring, issues related with carbohydrate counting, non acceptance by elderly and adolescent population throw a formidable challenge to explore more convenient yet effective regimen.

Research needs to be directed towards production of basal insulins with longer duration of action to provide 24 hours basal supply while preserving the advantage of once daily administration. Another exciting area could be development of insulins combining both basal and prandial components together. This should provide the benefit of starting and staying on one insulin and thereby make insulin regimen extremely user friendly that could be implemented with ease by majority of primary care physicians.

Certainly oral insulin will continue to charm the researchers and eagerly awaited by diabetic subjects.

INTRODUCTION

Majority of type 2 diabetics require insulin administration at some stage in their natural history. This could be necessitated either as a result of OAD (Oral Antidiabetic Agents) failure or to cover certain situations, which by their nature require insulin administration (Table-1). Several guidelines are available for insulin initiation and intensification; including Indian guidelines (1), ADA/EASD consensus statement (2), AACE guidelines (3), IDF guidelines (4), NICE guidelines (5), Canadian guidelines (6), Malaysian guidelines (7) ICMR guidelines (8) etc. Unfortunately all these guidelines differ in their recommendations in several respects. The issues at stake are the indications for insulin initiation, type of insulin to be administered for initiation, indications for intensification and insulin regimen to be used for intensification.

Glycemic control in countries following these guidelines still remains far from satisfactory. Average HbA1c in USA is more than 8% and across the globe the situation is no better. Market research shows wide variability in treatment preferences across countries.

Table 1: Indications for Insulin in Type 2 Diabetes

<table>
<thead>
<tr>
<th>At Onset:</th>
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<tr>
<td>• Very high blood glucose values i.e.</td>
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<tr>
<td>• Fasting &gt; 250 mg/dl</td>
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<tr>
<td>• Post prandial &gt; 300 mg/dl</td>
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<tr>
<td>• HbA1c &gt; 9.0%</td>
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<tr>
<td>(If the newly diagnosed patient is having systemic infection, sepsis, acute myocardial infarction, unstable angina, diabetic ketoacidosis or has to undergo surgery or is pregnant)</td>
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<tr>
<td>OHA Failure:</td>
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<td>Poor glycemic control in spite of optimal dose of two or three OADs (from dose response curve it has been observed that 80% of the response comes with half maximal dose):</td>
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<td>• Fasting &gt; 150 mg/dl</td>
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<tr>
<td>• Random or post prandial &gt; 200 mg/dl</td>
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<tr>
<td>• HbA1c &gt; 8.5%</td>
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<tr>
<td>Co-Morbid conditions:</td>
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<tr>
<td>• Severe systemic infection or sepsis</td>
</tr>
<tr>
<td>• Acute Myocardial Infarction or Unstable Angina</td>
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<tr>
<td>• Diabetic ketoacidosis or Hyperosmolar state</td>
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<tr>
<td>• Diabetic Kidney Disease</td>
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<tr>
<td>• Pregestational or gestational Diabetes</td>
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different countries and across physicians within the same country. There could be several explanations for these differences in the approach and for inadequacy of the Glycemic control.

**INDICATIONS FOR INITIATION**

Indications for insulin initiation are based upon availability of investigations to the physicians. In economically developed countries HbA1c level remains the gold standard both for insulin initiation and intensification (2,3,4). There are several issues related to this practice. HbA1c is not widely available to large segment of Indian population and therefore the decision to initiate and intensify insulin has to be based upon fasting and/or post prandial glucose estimations in conjunction with clinical features. HbA1c measurement has also other limitation in the form of significant prevalence of hemoglobinopathies and other clinical situations which could affect the assay. Most important issue is inadequate standardization of the assay procedure in different parts of the world.

Indian guideline for insulin initiation is quite pragmatic as it provides the flexibility to initiate insulin on the basis of fasting and/or post prandial plasma glucose measurements in addition to the Hba1c levels (1). However the guideline is not clear regarding number of plasma glucose measurements required to initiate insulin therapy. Secondly this approach should not become an excuse for not popularizing Hba1c estimation across the country. Hba1c is a well validated investigation and can provide uniformity in decision making process as has already happened in several developed countries. Majority of the outcome studies are based upon Hba1c values.

Hba1c level to initiate insulin in case of OAD failure is usually recommended to be > 7.0% (ADA/EASD target). However most recommendations agree that if Hba1c level is more than 8.5 -9%, irrespective of the dose of OADs, insulin should be initiated particularly in combination with optimized dose of metformin. It has to be remembered that availability of Incretin based therapies including Incretin Mimetics and DPP IV inhibitors may influence treatment decisions in situation where Hba1c level is between 7.0 to 9.0%. Furthermore target Hba1c has to be individualized depending upon the age of the subject, duration of diabetes, presence of co-morbid conditions and individual subject's social and logistics considerations (2). Publication of ACCORD (9), ADVANCE (10) & VADT (11) trials have clearly brought out these issues and individualization of Hba1c target have appropriately been recommended in different guidelines.

Indian guideline including insulin initiation at the time of diagnosis is a welcome step. Benefits of early initiation of insulin have been established beyond doubt. In this situation recommendations regarding down titration need to be clearly spelt out as rapid reduction in the dosage may be required because of quick glycemic control on account of good beta cell reserve, rapid correction of glucotoxicity and control of infection and other aggravating factors. Early initiation of insulin must be done with prandial insulins or premixed insulins and perhaps never with basal insulin.

**TYPE OF INSULIN FOR INSULIN INITIATION**

Majority of the guidelines suggest insulin initiation with basal insulin. Notwithstanding the advantage of once daily administration, there are several limitations with this approach. Basal insulin provides good control of fasting plasma glucose; however the post prandial hyperglycemia largely remains uncontrolled. Post prandial hyperglycemia is an important determinant of overall glycemic control (12).As a natural corollary, less than 50 percent of diabetic subjects achieve glycemic targets either of less than 7.0 percent or even worse the stricter target of less than 6.5 percent. Second important limitation with basal insulin is inadequate 24 hours coverage as almost all of them including Detemir, Glargine and NPH show tailing of effect after 12-16 hours of administration. Third limitation with this approach is a rather high incidence of hypoglycemia which prevents clinicians from optimal titration of the dosage. Another limitation is unacceptable weight gain either as a result of the increased snacking due to fear of hypoglycemia, its pharmacological effect or due to improved metabolic control.

Several approaches could be adopted to address these limitations with basal insulins. Research could be directed towards production of basal insulin with longer half life providing true 24 hours coverage. This would provide better glycemic control, yet preserving the advantage of once daily administration. Even better, molecules could be developed combining basal and prandial insulins providing simple and effective initiation and intensification with one insulin.

Insulin initiation could be done with pre mixed insulins which control effectively both fasting and post prandial hyperglycemia. Clinical trials and observational studies have shown superiority of pre-mixed insulins over basal insulins in achieving glycemic targets without increasing the risk of hypoglycemia (13, 14, 15, 16). Pre mixed insulins have another advantage of starting and staying on the same insulin, providing confidence and ease of administration and titration (17). It has been the experience of most clinicians that multiple dosages of insulins are eventually required to achieve 24 hours glycemic control. At least in insulin naive patients 3 doses of pre mixed insulin provided comparable glycemic control as compared to more complex basal bolus regimen (18).Physicians and subjects both fear the complexities involved with insulin regimens and eventually make this an excuse for inordinate delay in insulin initiation and insulin intensification. On the flip side, premixed formulations do not have the flexibility of titration of the rapid acting component as required by prandial glucose excursions. This limitation could be addressed by the use of 'high mixes'.

Premixed formulations are generally available as 30/70, 25/75 or 50/50 combinations of rapid acting and intermediate acting insulins. It is of common experience that these combinations are quite good for fasting plasma glucose control and are better than basal insulin in terms of post prandial control. However they still are inadequate in controlling the post lunch and pre dinner glucose excursions. Pharmacokinetic, pharmacodynamic and clinical studies show that high mixes with ratio of 50/50 or
70/30 combinations administered in the morning before breakfast or in few cases both before breakfast and lunch could overcome this inadequacy. More data needs to be generated before this could be accepted with confidence. It should however be clearly understood that these high mixes are not suitable for night dose of insulin as they provide poor control of fasting plasma glucose and increase the risk of nocturnal hypoglycemia. For night time dosage, pre mixed insulin with 30:70 ratio of rapid acting and intermediate acting insulin is most appropriate.

Irrespective of the type of insulin selected for initiation, titration algorithms are based upon self monitored plasma glucose values. These algorithms generally suggest a minimum of 3 recordings over the previous week and up titration is done on the basis of the lowest of the three measurements. (Table 2). This approach is good to minimize the incidence of hypoglycemia. However titration based upon an average of 3 measurements over last week or just previous day’s fasting plasma glucose could lead to better glycemic control. This may be at the cost of higher incidence of hypoglycemia. With evolving innovations in insulin molecules it might become feasible to titrate more aggressively to achieve the glycemic targets without increasing the risk of hypoglycemia.

Titration algorithms have to be conducive not only for good glycemic control but should also be able to minimize the incidence of hypoglycemia. It is of vital importance to incorporate clear recommendations for subjects who cannot afford self monitoring of blood glucose for financial and logistic reasons. Whether weekly or even fortnightly or monthly adjustment of insulin dosage based upon laboratory measurements of fasting and/or post prandial plasma glucose can provide reasonable degree of glycemic control to vast majority of diabetic subjects has to be an area of extensive research. With 57 million diabetics on board and still counting, India is already known as the diabetic capital of the world (19,20).

**INSULIN INTENSIFICATION; INDICATIONS AND REGIMENS:**

Initiating insulin is a big step forward. However this is not an end in itself. Clear recommendations are needed to clinicians with respect to the basis for insulin intensification and the appropriate regimens to be used for intensification. The most important issue is to understand that dose increase (dose optimization) should not be construed as intensification. Intensification means clearly a change in the insulin regimen that has to be more potent in terms of efficacy and also in terms of number of injections.

There is consensus among all guidelines that subjects not achieving target HbA1c with basal or pre-mixed insulins need to intensify their insulin regimen. The gold standard for insulin regimen is basal bolus therapy combining one or two doses of basal insulins and three doses of rapid acting insulins to cover the post prandial peaks following three major meals. Notwithstanding its sound scientific basis and clear superiority; basal bolus regimen is quite cumbersome for the diabetic subjects and 4-5 injections a day is generally not welcome. On the other hand, premixed insulins as intensification option have the advantage of one, two or three doses as compared to 4 or 5 dosages in the basal bolus regimen. However as mentioned earlier subjects not achieving post breakfast and post lunch glycemic control with pre mixed formulations might require high mixes in the morning and lunch time. Insulin dose in any intensified regimen needs to be titrated on the basis of self/laboratory measurement of fasting and post meal blood glucose levels. Whatever algorithm is used for initiation and intensification, one clearly needs to understand that titration has to be careful once you are approaching the target to avoid hypoglycemia as far as possible. Physicians, diabetic educators and subjects should be aware of the need and method of down titration and at times of withdrawal of insulin therapy.

Titration algorithms differ very significantly in different guidelines. It is of vital importance that these differences have to be understood in the background of different food habits and anthropometric differences amongst various populations. The fundamental issue remains excellent glycemic control without increased risk of hypoglycemia and weight gain.

**CONCLUSION**

Insulin initiation and intensification is indeed a challenging task. Insulin guidelines need to be very flexible and pragmatic both in terms of insulin regimens and with respect to the type of insulin administration. It should take into account the variations in the affordability and availability of different insulins and self monitoring of blood glucose (SMBG). This should enable greater proportion of the diabetic population to achieve their glycemic target and thereby minimize the long term complications with their enormous financial and medical consequences. If a given subject can afford only human insulin and may be only monthly estimation of plasma glucose value, he or she should still not be denied of the huge benefits of insulin therapy.

Insulin guidelines must cater to the needs of primary care physicians, as they will continue to treat the vast majority of the diabetic population. They have to be empowered with knowledge about insulin guidelines and regarding benefits of insulin therapy. They must be convinced that these guidelines could be implemented easily in practice as they are not too complex and do not require a big team.

**REFERENCES**


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