INSULIN INTENSIFICATION IN TYPE 2 DIABETES

What are the available/recommended strategies for insulin intensification?

It’s very important to start insulin in a patient with type 2 diabetes but it’s also important to understand that starting insulin is not enough. Because of the very nature of the disease which is that of a progressive decline in the beta cell function, physicians have to have evolving strategies over time, over the entire natural history of type 2 diabetes to keep the glycaemic targets under control.1 One of the strategies which is normally employed, mostly in the eastern part of the world, is starting with twice-daily premix insulin.2 But in the majority of the western world – Europe and America – the insulin initiation is done with once-daily basal insulin.1, 3 And then it depends upon whether you started on a basal insulin or a premix insulin, you would need to intensify the treatment. It’s important to understand that basal insulin initiation is a very good strategy but it does not take into account the issue of postprandial hyperglycaemia.4 And it’s very important to understand that the first abnormality in type 2 diabetes is loss of first phase insulin secretion leading to postprandial hyperglycaemia.5 So if we do not address the issue of postprandial hyperglycaemia, we leave glycaemic control less than optimal and that is not desirable. And therefore it could be a good strategy to initiate or intensify with a premix insulin. It’s also important to understand that initiating insulin is not enough. We have to optimise and then intensify. Physicians must understand this difference; that before intensifying you must optimally use the doses which are recommended for a particular insulin initiation regimen. Say for example, if somebody has been started with a basal insulin and the fasting plasma glucose is not on target, there is no point in shifting for intensification. We should first optimise the dose of the basal insulin and then only we should have the next strategy and that is of insulin intensification. We have a number of options to intensify. If a patient has started on a basal insulin, we can add one or two prandial insulins and this regimen is called basal plus regimen. The second strategy is that we can use twice-daily or thrice-daily premix insulin and the final – and the most important maybe, what is supposed to be the gold standard – is the basal bolus regimen where you are using one or two injections of a basal insulin and you are covering all the three meals with the prandial injections. So these are the three different intensification strategies that we are talking about in terms of insulin intensification.

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What is the current evidence for intensification with premix insulin vs. basal-plus (1–2 mealtime insulin injections)?

Insulin intensification either with a basal plus strategy or with a premix twice-daily administration are the most acceptable methods of insulin intensification across the world. In the basal plus regimen, we are using one long acting basal insulin and then one or two injections of the prandial insulin, identifying the largest glycaemic excursion or identifying the largest meal of the day. Whereas in the twice-daily premix
Insulin intensification can be done with twice-daily premix insulin and at the same time, can be done by the gold standard basal bolus regimen.\textsuperscript{10, 11} It’s important to understand the differences between these two regimens. In the twice-daily premix insulin, you are using the same insulin and you are using only two injections a day. Where as in the basal bolus regimen, you are using two different types of insulin – one or two injections of basal insulin and three injections of prandial insulin.

At the same time, when you are using a basal bolus regimen, you are talking about using the concept of carbohydrate counting which is extremely difficult to be handled by majority of the primary care physicians across the world. And at the same time, when you are using a basal bolus strategy, you are asking your patients to do a lot of self-monitoring of the plasma glucose. That not only is irksome to the patient\textsuperscript{12}, but at the same time is quite expensive for the patients. When we look at the clinical data comparing these two different regimens, we have got very clear answers to these questions. In one of the famous study called the PREFER Study conducted by Andreas Liebl in Germany, he compared this twice-daily administration of BIAsp30 with 4 or 5 injections a day of insulin detemir once or twice a day with three injections of insulin aspart – the full blown basal bolus regimen. And the results showed that those patients who were insulin naïve (who never used insulin in the past), there was no difference in the glycaemic control between these two regimens. On the other hand, those subjects who were already exposed to insulin treatment, certainly there was better glycaemic control with a basal bolus regimen.\textsuperscript{13} And therefore we can actually come to the conclusion that a large number of patients of type 2 diabetes can actually have insulin intensification with twice-daily administration of premix insulin rather than going to
Insulin intensification with three-times daily low mix BIAsp 30 or utilising high mixes - which means 50 per cent of a rapid acting insulin and 50 per cent of the basal insulin - are important strategies in insulin intensification. However it’s important to understand the pharmacokinetic and the pharmacodynamic differences between these two regimens. When we are talking of using high mixes three times a day, for the morning and the afternoon injection it is perfectly alright, but when you look at the pharmacodynamic effect, because of the 50 per cent rapid acting insulin, you are likely to see a significant reduction in the risk of hypoglycaemia. 16 So certainly, thrice-daily administration of premix insulin is a good intensification option. And the issue is that when you are comparing these two different regimens, you are actually doing away with the concept of carbohydrate counting. Physician across the world are not very conversant and are not very happy to bring into their practice the concept of carbohydrate counting. And when physicians are so reluctant, we can imagine how the patient would actually accept the concept of carbohydrate counting. So all in all, when we compare these two regimens, thrice-daily administration of premix insulin is a very simple method if intensification, more acceptable to the patient, reduces the cost of monitoring without compromising the quality of glycaemic control or increasing the risk of hypoglycaemia.
to produce nocturnal hypoglycaemia, particularly in the middle of the night. And at the same time – because you only have 50 per cent of the long acting insulin – your fasting plasma glucose is not going to be adequately controlled. So you are compromising on the fasting plasma glucose control and increasing the risk of nocturnal hypoglycaemia. Once we have understood this pharmacokinetic and (pharmaco)dynamic differences then we have to look at the studies to compare these two different regimens. And obviously in all these studies, the incidence of hypoglycaemia is always more with the high mix strategy. Having understood this, it’s also important to understand that there would be a subset of patients with type 2 diabetes where thrice-daily administration of premix insulin of the low mix variety – that is 30/70 – has not been able to control the postprandial hypoglycaemia. That could be related to the ethnic variability because we know that Asian people particularly have got very large area under curve for the postprandial glycaemia and therefore in those subset of patients it would be important to utilise the high mix strategy, at least in the morning and at lunchtime. But even in this regimen, it would be scientific and prudent to understand that the night doses should be that of a low mix. That obviously brings this complexity that now you are using two different types of insulin, whereas if you are using thrice-daily low mix then you are using the same insulin and the patient’s acceptance and execution of the insulin strategy is quite easy.

References


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