INSULIN TREATMENT IN TYPE 2 DIABETES

ISSUE 1

Should postprandial glucose be addressed from the start in type 2 diabetes management?

Postprandial glucose must be controlled very early in our treatment management. When we look at healthy individuals we can see that postprandial glucose is very closely regulated. Normally we do not see values above 7-8mmol/L which is around 140mg/dL. As soon as diabetes comes into being, we see a lack of first phase insulin. With this lack of insulin - of fast acting first phase insulin - the postprandial glucose is going up, as one of the first features of type 2 diabetes. Together with the postprandial glucose, HbA1c is going up. Nowadays we have strict HbA1c targets: below 7%, and in order to reach these targets, we really have to control the postprandial glucose, because in the lower range of HbA1c, postprandial glucose plays a much greater role than fasting plasma glucose. So you have no chance to reach the targets if you do not control the postprandial glucose. But it’s not only because of HbA1c that we try to control the glucose excursion after the meal; another fact is that we have a couple of studies showing that there is a clear and independent association between the rise of postprandial glucose excursions, and cardiovascular risk markers. Like for example: intima-media thickness, oxidative stress or endothelial dysfunction. And moreover, from the Decode study, we know that the mortality in type 2 diabetes is also associated to the postprandial glucose. Knowing all that, it is clear that the IDF – the International Diabetes Federation – in it’s guidelines for postprandial glucose has recommended a strict target for postprandial glucose which is below 9mmol/L or 160mg/dL and this has to be achieved from the very beginning.

ISSUE 2

How does the complexity of an insulin regimen affect diabetes management?

The complexity of a therapy, for example of insulin therapy, is one of the key factors for success or failure of our therapies. When we look at our patients with type 2 diabetes we can see that many of them do not reach their glycaemic targets. When we look at the fact as to why they don’t reach their targets, we can see that treatment adherence is poor in many of them. And there are a couple of factors which are responsible for poor treatment adherence. This may be side effects, this may be cost of therapy, but very often its complexity of therapy. Especially insulin therapy is considered to be very complex, very difficult, and very burdensome. With insulin there are some factors which contribute to complexity and one is the number of injections per day. Another factor is that when the patients have to use human insulin, then they have to wait after the injections at least thirty minutes until they can eat, and this is something patients simply don’t do. And it makes the...
therapy complex, and difficult, and finally unsuccessful. When we ask our patients and the physicians what the ideal insulin would be; they say, that it has to be an insulin which is easy to start, they want to have a small number of injections per day, and they want to cover the prandial and the basal needs with one injection only. And they want to have an insulin which is very easy to intensify as well. 19

**ISSUE 3**

What do guidelines suggest for insulin initiation and intensification?

There are numerous guidelines, national guidelines, international guidelines for diabetes treatment and of course also for the initiation and intensification of insulin therapy. Probably the most popular and commonly used guidelines are the guidelines published by the IDF (the International Diabetes Federation) and the position statement published by the European EASD and the American ADA. 20, 21 Both of these guidelines recommend strict HbA1c targets which is, as an average below 7% in our patients, and of course this has to be individualised in each patient. Now when we come to insulin, and we look at the ADA/EASD position statement, insulin should be started at each step of the treatment flow whenever it’s necessary, whenever the targets cannot be reached with oral anti-diabetic agents. And let’s look at the type of insulin which is recommended. 20

In the ADA/EASD position statement, it’s generally recommended to start an insulin therapy using basal insulin. And then as a second step, short acting insulin is added which ends up in a multiple dose injection therapy, three or four injections per day, which of course is very flexible but also very complicated for many patients and it’s a burden for most of the patients. On the other hand, in the same publication by Inzucchi, it stated that if the postprandial glucose is an issue, if it’s elevated, then another option is to start insulin therapy with premix insulin. The premix insulin can be used to start a therapy with insulin and to intensify the insulin therapy so it stays a more simple kind of therapy, easy to do, maybe not so flexible, but very easy for patients. 20

When we look at the IDF guideline they recommend to start an insulin therapy as basal insulin once daily, or premix insulin once or twice daily. And please remember in the postprandial glucose guidelines by the IDF, it’s clearly stated that we have to keep a target postprandial glucose below 9 mmol/L or 160mg/dL and this of course is easier to reach using premix insulins, especially premix analogue insulins. 21

**ISSUE 4**

What is the role of premix analogue insulin in the management of diabetes?

The interesting thing with premix insulin in general is that we have a short acting component, and an intermediate acting component in one insulin, in one formulation. And when we look at efficacy, at safety, and at convenience this is maximised when we have a premix analogue insulin, like for example BIAsp 30. With BIAsp 30, we have a huge experience. 22 It has been launched more than twelve years ago, 22 roughly 2.6 million patients are treated with this insulin currently, 23 and we have nearly fifty publications, scientific work, randomised controlled studies, observational trials on this insulin. 24 So you see the safety and the efficacy has been proven in a lot of experience. So when we look at BIAsp 30, we can say that we have an ideal coverage of the prandial part. 25 We have a coverage of the basal demands as well, and this insulin can be started very easily. It can be initiated once daily or twice daily. 26, 27, 28, 29, 30 It can be intensified very easily, with the same insulin, with the same pen. 31
BIAsp 30 is a mixture of 30% soluble insulin aspart, and 70% insulin aspart which is crystallised with protamine. Let’s first look at the fast acting component, at insulin aspart. Insulin aspart differs from human insulin, just one amino acid has been exchanged and this actually leads to an insulin which is monomeric in contrast to human insulin which comes as hexamers. Hexamers are large and complex and they are absorbed very slowly from the subcutaneous tissue.32 The monomeric insulin, the insulin aspart, is absorbed rapidly from the subcutaneous tissue and the glucose lowering effect therefore, is much faster and stronger as well which means better postprandial glucose with the short acting analogue.33, 34 Another fact is that the duration of glucose lowering is shorter as well, and this minimises the risk for hypoglycaemia. Another advantage is that also it’s more convenient because it can be injected immediately before the meal, or even after the meal if necessary, and this is very valuable for many of our patients.34 With human insulin you have to wait at least for thirty minutes after the injection before you can eat.35

When we want to find out about the role of therapies of insulins, we have to look at studies. On the one side we have randomised controlled studies - RCTs - these are certainly the gold standard in our evidence based world. But they are somewhat artificial. We have a highly selected population of very compliant patients and we have highly regulated procedure. This is not daily life. Therefore, observational trials are getting more and more important.36, 37 Observational trials are really a look over the shoulders of the physicians and the patients, and they are real life. In observational trials we have a large number of patients, normally tens of thousands, and this allows us to detect early and very rare complications as well. So, observational trials are a kind of additional information to the randomised controlled studies, although there may be some bias and some confounding factors but we have to see both kinds of trials together.36, 37 Now let’s look at observational trials with BIAsp 30, and I would like to mention three important studies. The first is the IMPROVE study. The IMPROVE study was a large observational trial with more than 50,000 patients with type 2 diabetes and they had been switched to BIAsp 30 or started newly on BIAsp 30. And of these patients, 53% actually reached the target of HbA1c less than 7% which is an excellent result for daily life. And at the same time, the risk for severe hypoglycaemia dropped for 94%.38 The second study is the PRESENT study. The PRESENT study is a study on more than 20,000 patients with type 2 diabetes and they also were either started on BIAsp 30 or switched to BIAsp 30. In this study, there was a vast drop in HbA1c; those who were insulin-naïve, dropped their HbA1c by 2.2%. Those who had already been treated with other insulins, dropped by 1.6% and at the same time, the risk for hypoglycaemia did not increase, although the level of glucose was much lower.39 And finally, we have the A₁chieve study, the largest observational trial in the field of diabetes which has ever been conducted. More than 66,000 patients were included. 63.5% of these patients actually were treated with BIAsp 30, and again very good results as to HbA1c reduction and very low risk of hypoglycaemia was shown in this study.40 So, when we take together the randomised controlled studies and the observational trials, it’s fair to say that BIAsp 30 is an insulin with a high efficacy and a very good convenience as well.38, 39, 40
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