INSULIN INITIATION IN TYPE 2 DIABETES



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As well as clinical diabetes, Dr Wu has a long-term interest in both teaching and research. As the Director of the Health Professional Training and Development Unit within the Diabetes Centre at the RPA Hospital, Dr Wu formulates and delivers novel online-based educational programmes in clinical diabetes. These have included CD-ROM-based, internet, radio, teleconference, social media and interactive webinar initiatives. He has also been instrumental in establishing the RPA Diabetes Centre as the first International Diabetes Federation Centre of Education in Australia. In addition, Dr Wu is the Director of Physician Training at RPA Hospital and is responsible for overseeing the postgraduate education of junior medical officers across the RPA network of hospitals in the state of New South Wales.

This text is derived from the insulin initiation video presentation by Dr Ted Wu and includes all relevant references



What are the available/recommended strategies for insulin initiation and does biphasic insulin have a place in these recommendations?

Insulin therapy is often required in type 2 diabetes mainly because type 2 diabetes is a disease of progressive beta cell failure. Whereas a patient may have been well treated with oral monotherapy, often over time they need to progress onto different and additional oral therapies and eventually even these will fail.[1,2] It is at this point that the body is not making enough insulin from its beta cells and we need to replace the missing insulin with exogenous insulin. When this should take place is earlier than we had previously realised.[3] Both the DCCT and the UKPDS long term follow up studies showed us that early good glucose control is of vital importance. These studies showed that very good glucose control early on in the early duration of type 2 and type 1 diabetes led to massive benefits in terms of complications later on.[4] Whereas the ACCORD Study showed that where the complications already exist, then the sudden intensification, or lowering of HbA_{1c} did not do very much to the final outcomes.[5] When we are thinking about starting insulin, we need to think about both the fasting sugar and the postprandial sugars because we have come to realise that postprandial sugars are as important if not more important than fasting sugars, and in addition to this, postprandial glucose may be raised even in the context of normal fasting sugars.[6] Therefore when we start insulin, we have to target the abnormalities that are present in a patient and sometimes, in fact often, the postprandial glucose is as important as fasting glucose. Therefore we need to choose therapies that target both PPG and FPG and premix insulin is one such therapy that targets both at the same time. Because of this the American Diabetes Association and the European Association for the Study of Diabetes have in their guidelines premix insulin as well as basal insulins as the starting options when initiating insulin.[7] And this concept of postprandial glucose being important has reached such significance that the International Diabetes Federation have their own guidelines that target specifically postprandial glucose. Therefore when we think about starting insulin we have to think about not just fasting glucose but also postprandial glucose and premix insulin gives us the opportunity to target both at the same time.



Is once-daily biphasic insulin aspart 30 suitable for insulin initiation?

Biphasic insulin aspart 30 is a useful option for initiating insulin therapy, especially once daily. This affords convenience as well as control of postprandial and fasting glucose with a single injection.[8] How does this work? Well, as we all know biphasic insulin aspart 30 is a mixture of rapid acting analogue and as well as intermediate acting insulin and if given at the main meal of the day, can target the postprandial sugar of that meal as well as the basal requirements – let's say overnight if given with the evening meal. Now is there any evidence that this is useful or in fact is effective? There are several studies which show the benefit of once-daily biphasic insulin aspart 30. For example, the OnceMix Study is the study of about 400 patients which compared glargine at night time to biphasic insulin aspart 30 given once a day with the evening meal. The oral hypoglycaemics were continued and in this study, the biphasic insulin aspart 30 once-daily showed superior HbA_{1c} lowering to that of once-daily glargine. Somewhat surprisingly to some people, the fasting control was equivalent in both but what was different was that the postprandial or evening blood sugars were much lower for the group that were taking the biphasic insulin aspart 30. Now remember, these were both equivalent in terms of numbers of doses of insulin and the numbers of insulin required and therefore there was equal convenience for both groups. But the biphasic insulin aspart 30 group did better in terms of glucose control. In terms of hypoglycaemia, there was not much difference but there was slightly greater rates of nocturnal hypoglycaemia for the biphasic insulin aspart 30. However the rates of hypos were low in both groups.[9] There was a separate study called the 1–2–3 Study which looked at initiating with once a day biphasic insulin aspart 30 then going to twice a day or three times a day if once was or was not enough. And in this case, more than twenty per cent of people started on once a day biphasic aspart insulin 30 and stayed on that with very good glucose control.[10] Another question that often arises is should we continue the oral hypoglycaemics when we start once-daily biphasic insulin aspart 30? And the answer to that is yes. It's very useful, especially to continue the metformin as this will provide some decrease in insulin resistance. But it's also useful to continue the sulfonylureas during the day which gives us better postprandial control during the day and there's also evidence from studies such as the Sit2Mix Study that sitagliptin plus metformin and biphasic insulin aspart 30 once-daily is also a very good combination.[11] And therefore, initiating with once-daily BIAsp 30 is a viable and preferable option in a lot of patients.



Is twice-daily biphasic insulin aspart 30 suitable for insulin initiation?

Initiation of insulin with BIAsp 30 can be done either once-daily or twice-daily. Twice-daily is certainly also a very valid starting point. There's much evidence to show us that starting with BIAsp 30 twice-daily is very effective in bringing HbA_{1c}. For example, the INITIATE trial was a large trial done in people with type 2 diabetes with poor HbA_{1c} control and they were started on either once-daily basal insulin or twice-daily BIAsp 30. In this study, the patients who had BIAsp 30

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twice-daily had HbA_{1c} that were as much at 0.5 per cent below that of the people who started on basal insulin. In addition to this, while the fasting glucose control was equivalent in both groups, the post-prandial or post meal sugars in the group that started BIAsp 30 twice-daily was better.[12] Another study which tends to show us that BIAsp 30 twice-daily is a very good starting point is the PREFER Study which took both insulin naïve and people already on insulin and they randomised them to either basal bolus insulin or to twice-daily BIAsp 30.[13] Now remember the comparator group here was basal bolus insulin which is the most intensive and yet troublesome or cumbersome regimen to use insulin. And most people would have said that the basal bolus insulin would have done much, much better than BIAsp 30 twice-daily. However in the insulin naïve group – that is those people who had never taken insulin before – the group that took BIAsp 30 twice-daily did just as well as the group that went onto basal bolus insulin.[13] And thus, in the initiation phase of insulin, BIAsp30 twice-daily is very good in terms of convenience because it is one insulin, one pen, just given twice-daily and yet can be as effective as even basal bolus insulin.[14]



What are the primary challenges of insulin initiation?

There are sometimes some barriers in the way when we think about starting insulin. And we can break this down into patient-related barriers and physician-related barriers. In terms of the patient-related barriers, there is sometimes some stigma involved in starting insulin or a perception that somehow they are failing their treatment and this is why they need to start insulin. But more than that, patients fear things such as the hypoglycaemias and the weight gain that may occur when insulin is started.[15] Physician-related issues are somewhat different. While physicians are worried about these issues such as hypos, physicians are additionally worried about things such as additional complexity of treatment, adherence or compliance to the treatment and how the patient will perceive the initiation of insulin itself.[16] Some of the ways to overcome these barriers are to think about discussing insulin early on. We know that type 2 diabetes is a progressive disease and that some 50 per cent of patients will probably need insulin within about 6 or 7 years of diagnosis.[17] And therefore we tend to start to discuss insulin earlier rather than later and we couch it in the terms of insulin being the most effective treatment, the best way to bring down blood glucose and HbA_{1c} rather than a signal for failure. Other barriers such as hypos should be addressed head on because, again, if we discuss these things and recognise them and also in our mind, utilise the insulin in the best way, we can minimise the hypos but more importantly, minimise the fear of the risk of hypos. In terms of the weight, we know that the higher your HbA_{1c} when you initiate the insulin, the more weight you tend to gain[18] and therefore that's another reason why we tend to initiate insulin earlier rather than later. The last point is that of complexity and I think this is a very real one. There is much evidence to show us that increasing complexity of regimens does lead to decreased adherence to treatments[19] and if we think about different sorts of insulin treatments – there is basal bolus insulin with two different types of insulin, two different devices, up to five injections a day versus premixed insulin such as BIAsp 30 which can be initiated once a day, which can be intensified simply to twice a day with the one device or even three times a day, again with the one single type of insulin. So while there are barriers to starting insulin, we need to think about ways that we can overcome these barriers. Fortunately, there are many, many strategies that we can utilise to decrease these barriers.



What recommendations are available to doctors to make insulin initiation easier and to help patients self-manage their treatment successfully?

I think one of the keys to these recommendations of how physicians can best initiate insulin, really need to go back to the very basics at the very start. I think we need to educate our patients early on that insulin is often necessary in type 2 diabetes and is often the most useful method that we have to control blood glucose. We need to de-stigmatise insulin, we need to de-mystify insulin and so therefore patient education is paramount, early patient education is very, very important.[20] When thinking about initiating insulin, we also have to think about what sort of insulin we are going to start. There are many different types of insulin and both the ADA and EASD tell us that initiating with basal insulin analogue or with biphasic insulin aspart or other premix insulin is usually the common way to start insulin.[21] So which one should we use? We need to go back and think about the patients. Patients have high HbA_{1c} because they have high fasting glucose, high postprandial glucose or both. And in patients with high fasting glucose only, I think that yes, we can start basal insulin but I think that a lot of people have high postprandial glucose. And if you have high postprandial glucose, then I think that basal insulin alone is often not enough to treat that problem. And you need something like premix insulin to target both the PPG and the FPG. There's a lot of evidence to show us that postprandial glucose can be very harmful for patients in terms of hard outcomes such as mortality even in isolation. You can have perfectly normal fasting glucose but high postprandial glucose will lead to bad outcomes and therefore postprandial glucose is worth controlling (Table 1). And therefore if we are to think about initiating insulin, we have to think about something which targets PPG as well as FPG. [22, 23] This is such an important point that the IDF have a set of guidelines that are targeted just at postprandial glucose. And in those guidelines, they also suggest that premix insulin is a very good way to initiate insulin therapy.[24]

Table. 1. IDF evidence statement and recommendation for post-meal and post-challenge hyperglycaemia[6]

EVIDENCE STATEMENTS
Post-meal and post-challenge hyperglycaemia are independently associated with the following in people with diabetes: • macrovascular disease [Level 1+] • retinopathy [Level 2+] • cancer [Level 2+] • impaired cognitive function in elderly people with type 2 diabetes [Level 2+] • increased carotid intima-media thickness [Level 2+] • decreased myocardial blood volume and myocardial blood flow [Level 2+] • oxidative stress, inflammation and endothelial dysfunction [Level 2+]
RECOMMENDATION
Postmeal hyperglycaemia is harmful and should be addressed
Level 1+ is based on well conducted meta-analysis and systematic reviews of randomised clinical trials. Level 2+ is based on well conducted case control/ cohort/ basic science studies with a low risk of confounding bias and a high probability that the relationship is causal

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What are the barriers and challenges of physicians for insulin initiation? What are your recommendations to overcome these barriers?

Insulin is a very important and effective treatment for diabetes and yet there are many barriers and challenges that physicians face when they try to initiate insulin in their patients, especially with type 2 diabetes. Some of the barriers that physicians might come across are things such as the patient's perceptions, the time that is required to initiate and follow up as well as aspects such as weight gain, as well as hypo risk and finally, complexity and adherence issues.[25] If we finally do identify these barriers, then we need effective mechanisms to overcome these barriers. In terms of patient perception, I think that we need to highlight to our patients early on that about 50 per cent of people with type 2 diabetes require insulin after about 6 years or so of duration of type 2 diabetes.[26] We also need to point out that insulin is not a failure, but in fact insulin is the most effective treatment that we have for hyperglycaemia. In terms of weight gain, one effective way to minimise weight gain is to start insulin early rather than later. We know that the higher the initial HbA_{1c} before starting insulin, the more weight people tend to gain.[18] Therefore this speaks to the need to initiate insulin earlier rather than later. In terms of hypos, it is fortunate that we have very good modern insulins such as insulin analogue BIAsp 30 which minimises the risk of hypos as compared to the previously available human insulins, whether premixed or non-premixed.[27,28] Also by increasing physicians' education, by resources such as this or conferences, physicians can help minimise the risk of hypoglycaemia in our patients. Lastly, in terms of complexity, there is no doubt that increasing complexity leads to decreasing adherence for our patients.[29] Once again, fortunately, premix insulin can be started either once-daily, can be started twice-daily and if necessary, intensified to twice-daily or even three-times daily with the simple one device, one insulin regimen. By giving the patients the simplest regimen possible, we maximise the potential for adherence.

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