When to Start Insulin Treatment for Type 2 Diabetes Patients?

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Type 2 diabetes is a common disease due to relative insulin deficiency and usually runs a deteriorating course due to a gradual deterioration of beta cell function. At the time of diagnosis, relative beta cell function is on average only 55% of normal and continues to decline at a rate of 4.5% per year. This is translated into a gradual rise in HbA1c in diabetes patients. The recent ADOPT study showed that by using insulin sensitisers, the rate of rise in HbA1c could be markedly reduced from 2.4% per year with sulphonylurea to 1.2% per year with metformin and 0.7% per year with rosiglitazone. However, zero deterioration in the long run has not yet been achieved up till now. Therefore, one can expect that almost every diabetes patient will need insulin if they survive long enough. This has been well demonstrated in the UKPDS study, in which multiple therapies including insulin were needed as disease progressed. The recent ID MPS study, which was a clinic based survey of diabetes patients, showed that 31% of Type 2 diabetes patients were on insulin treatment.

Insulin can be used to control hyperglycaemia almost in any stage of Type 2 diabetes. However, there are some situations in which insulin treatment has been demonstrated to be more favourable than other treatments. These include severe hyperglycaemia at the time of presentation, oral hypoglycaemic agent failure, stress related hyperglycaemia and in situations in which oral hypoglycaemic agents are no longer safe, such as moderate to severe renal impairment. In this article, we will concentrate on the first two situations which are more relevant to primary care.

Due to delayed presentation, a significant proportion of Type 2 diabetes patients have rather severe hyperglycaemia at the time of presentation. These patients are usually characterised by poor beta cell function and are in fact at a later stage of the disease. A study conducted in China looked at the effects of different modalities of treatment in this group of patients. The subjects in this study were a group of newly diagnosed Type 2 diabetes patients with a mean HbA1c of 9.5%. They were randomised into three groups, namely the insulin pump (CSII), the multiple injection (MDI) and the traditional oral hypoglycaemic agents, namely sulphonylurea and metformin. Their treatment was titrated to reach near normal glycaemia and such treatment was maintained for 2 more weeks after glycaemic target had been reached. Then they were taken off pharmacological treatment and the progression of disease was defined as fasting glucose above 7.0 mmol/l. At one year, around half of the subjects received insulin treatment previously could be maintained on life style modification alone, whereas only 25% of those having had received oral hypoglycaemic agents could be maintained on life style modification alone. This study, though not fully compatible with our usual practice, pointed to the important concept of prolonged protective effects of early insulin treatment. In fact, the above mentioned study showed that subjects receiving insulin treatment had greater improvements in beta cell function when compared with oral hypoglycaemic agents, possibly due to resolution of glucose toxicity. It should be noted that UKPDS, a long term landmark trial in diabetes also compared the treatment effects of insulin with other oral agents and came to the conclusion that early insulin treatment did not confer more benefit but caused more hypoglycaemia. However, there are significant differences between the two studies. Firstly, the study in China included diabetic patients with a mean HbA1c of 9.7%, whereas the mean HbA1c in the UKPDS population was 7.0% only. Secondly, the China study adopted much more aggressive treatment strategy using the insulin pump and multiple injections instead of the once daily intermediate acting insulin in UKPDS. Thirdly, UKPDS had a much longer follow-up of up to 10 years, while this study had follow-up data on up to one year only. Therefore, it remains unclear whether the differences in conclusions drawn from these two studies stemmed from the difference in target populations, or the difference in durations of follow-up. However, other studies with early use of insulin suggested that the benefit of insulin treatment may still be observed at two years. It is therefore more likely that the difference is mainly due to the difference in target populations.

The second situation in which insulin is frequently used is oral hypoglycaemic agent failure. However, it should be noted that this is a vaguely defined situation and can be interpreted in many different ways. First of all, the time of failure depends on the target HbA1c. Nowadays, ADA recommends HbA1c of below 7.0% as the target for most diabetic patients, which is a much more stringent target compared with the old days. Secondly, the number of oral agents used is not well defined in oral hypoglycaemic agent failure. In the early 90s, when sulphonylurea and biguanide were the only two classes of widely available anti-diabetic drugs, insulin was often used when the combination of both failed to control hyperglycaemia. ADA and EASD recommend that the use of insulin can be considered even as early as metformin failure. However, with the availability of more oral agents, the use of insulin
can often be delayed. There are studies showing that at the time of failure of both sulphonylurea and metformin, the addition of glitazone can provide similar glycaemic control compared with insulin.\textsuperscript{12-13} There are also studies showing that at time of failure of oral hypoglycaemic agents,\textsuperscript{21} the addition of glitazone can provide similar glycaemic control compared with insulin.\textsuperscript{12-13} There are also studies showing that DPP-IV inhibitors could be safely combined with metformin and sulphonylurea.\textsuperscript{14}

Therefore, whether oral hypoglycaemic agent failure should be defined as failure of 2 oral agents or three oral agents is still up to individual interpretation. And it remains to be proved whether earlier use of insulin at the time of 2 agents failure confers more benefits than the use of three oral hypoglycaemic agents. However, it should be noted that there are no large scale studies to support the combination of four oral agents, and the use of which should not be encouraged. It is often a misconception that insulin should only be used at the time of very severe hyperglycaemia and as a result insulin use is often delayed. Recently there was a study which looked at the use of insulin at the time of 2 agents failure but with a rather mild degree of suboptimal control.\textsuperscript{21} Three type 2 diabetes patients with HbA1c between 7-8%, on sulphonylurea and metformin were randomised to receive either lantus insulin or life style modification. As expected, the insulin treated group had HbA1c reduced from 7.6% to 6.8%. What was more encouraging was that there was a very low risk of hypoglycaemia despite that the glucose level before insulin treatment was not very high. Furthermore, in that particular study, the life style modification group had a reduction of 0.16% only despite successful weight reduction of 2.5 kg during the study.\textsuperscript{15} Therefore, in case of oral agent failure, one should not wait until very high glucose levels before insulin treatment is started.

Combination therapy of insulin with oral agents is the most often adopted regime in starting insulin treatment. The recent 4T-study looked at the effects of different regimes in the initiation of insulin treatment in patients not under good control with 2 oral agents. Three regimes were compared, including prandial insulin, basal insulin and premix insulin. After 3 years follow up, the regime with best glycaemic control, least hypoglycaemia and best patient satisfaction was to initiate basal insulin and followed by adding prandial insulin if the patient failed to reach treatment target.\textsuperscript{16} Studies also showed that long acting insulin analogues including insulin leemir and insulin lantus had less symptomatic and nocturnal hypoglycaemia compared with NPH insulin although both achieved similar HbA1c level.\textsuperscript{17,18} This is important in real life as the patients are less motivated compared with those in clinical trials, and hypoglycaemia will be one of the major barriers in initiating insulin treatment and achieving good glycaemic control. Insulin leemir has the advantage of less weight gain compared with other types of insulin, whereas lantus has the advantage of being more long acting.\textsuperscript{19-20} Furthermore, meta-analysis showed that in order to achieve a HbA1c below 7%, one should aim at a fasting glucose below 5.5 mmol/L, which is a more stringent level compared with those on oral hypoglycaemic agents.\textsuperscript{21}

Despite being a common treatment in type 2 diabetes, misconception about insulin is very common among not only diabetic patients, but also health care professionals. Insulin use has been labelled as a sign of non-compliance, linked to terminal disease and mislabelled as addiction. In a survey about insulin use in type 2 diabetes, only a quarter of the patients believed that insulin use could help them to achieve good glycaemic control and around half of them were worried about the need to start insulin. However, that study also showed that Type 2 diabetes patients treated with insulin had similar levels of motivation to comply with treatment compared with those not put on insulin. Therefore, once the patients have accepted insulin treatment, it seems the stress of treatment is less severe than one would have expected\textsuperscript{22}.

In conclusion, insulin treatment can be used at almost all stages of diabetes. In clinical practice, insulin treatment should be initiated if the patients have severe hyperglycaemia at the time of presentation or if the patients are not under good control even with the use of multiple agents. However, insulin treatment is often mislabelled and needs extensive explanation before one embarks on treatment.

References


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