

'Insulin should be prescribed at the outset of diagnosis of type 2 diabetes'

FOR

Dr Marie-France Kong

Consultant Physician, University Hospitals of Leicester NHS Trust, UK

Type 2 diabetes mellitus is a progressive disease characterised by continued gradual decrease in pancreatic beta-cell function, impaired insulin secretion, and increasingly severe insulin deficiency resulting in loss of glycaemic control over time, and most patients will ultimately require insulin therapy.^{1,2} Insulin secretion is ~50% diminished at the time of diagnosis of type 2 diabetes and continues to decline, at least in those treated with diet, metformin or a sulphonylurea.¹ Therefore insulin given at time of diagnosis is not too early. In clinical practice, treatment tends to follow a stepwise approach, beginning with diet and exercise, followed by the addition of one or more oral hypoglycaemic agents (OHAs) and the incretins with initiation of insulin therapy as a final step. Optimal disease management is patient-specific. When the initial presentation is one of marked hyperglycaemia, insulin may be the only way in which to get the patient anywhere near goal and to improve osmotic symptoms. Insulin can lower HbA_{1c} by $\geq 2.5\%$ compared to HbA_{1c} reductions of 0.8–2.0% with oral agents used as monotherapy, and therefore insulin therapy has the potential to decrease any level of elevated HbA_{1c} to, or close to, the therapeutic goal when used in appropriate doses.³ Early aggressive control with insulin may ameliorate beta-cell fatigue, improve pancreatic function and enable reduction or even withdrawal of insulin later. Other benefits of initiating insulin at the outset of diagnosis are reduction in pill burden, avoidance of polypharmacy and drug interactions, and improvement in lipid profile.

Study findings

The UKPDS demonstrated that early intervention to achieve tight glycaemic control resulted in a 25% reduction in the risk for microvascular complications.^{4–7} Reduction in risk of myocardial infarction was of borderline significance ($p=0.052$). Recent evidence, however, suggests that early good glycaemic control has a 'legacy effect' by preventing macrovascular events many years later (i.e. induces a 'metabolic memory').^{8,9} Post UKPDS trial, differences in glycated haemoglobin levels between treatment groups were lost after the first year. However, despite an early loss of glycaemic differences, a continued reduction in microvascular risk and emergent risk reductions for myocardial infarction and death from any cause were observed during 10 years of post-trial follow up.⁸ In addition, tight glycaemic control has also been shown to result in lower treatment costs in adults with diabetes¹⁰ – with every 1% increase in glycated

haemoglobin concentration over 6%, health care costs rise by 7% over the subsequent three years.¹¹ However, all too often insulin is still considered as 'last resort' or 'end-stage' therapy. A study reported that the HbA_{1c} level of nearly 1000 patients on combination OHAs was 9.2% (77mmol/mol) when insulin was started.¹² While on combination OHAs, these patients spent 30 months with HbA_{1c} levels more than 8.0% (64mmol/mol) and 58 months with HbA_{1c} levels more than 7.0% (53mmol/mol) prior to insulin therapy, exposing patients to prolonged hyperglycaemia and the increased risk of diabetes-related complications.

Further evidence

Early initiation of insulin can help lower insulin resistance, reverse glucotoxicity and lipotoxicity, improve both insulin sensitivity and insulin secretion, and preserve beta-cell function for longer than is possible with OHAs alone.^{13,14} There is increasing evidence suggesting that aggressive lowering of blood glucose with insulin therapy in newly diagnosed patients can result in sustained remissions (i.e. normoglycaemia) without the need for glucose-lowering medications.^{15–17} In a randomised, parallel-group study, 382 patients with newly diagnosed type 2 diabetes were randomly assigned to treatment with continuous subcutaneous insulin therapy, multiple daily insulin injections, or OHAs.¹⁷ Once patients achieved and sustained on-therapy normoglycaemia for two weeks, pharmacological treatment was stopped. Normoglycaemia was attained by >95% of patients in the insulin treatment groups compared to 84% of those receiving oral agents and in less time (4–6 vs 9 days). After one year, remission rates were significantly higher in the insulin groups than in the OHAs group (51.5% vs 26.7%; $p=0.0012$). In addition, the increase in acute insulin response was sustained in the insulin groups but significantly declined in the OHAs group at one year.¹⁷ Another smaller study ($n=20$) found an immediate improvement in beta-cell function after switching patients from sulphonylurea to pre-prandial rapid-acting insulin analogue therapy.¹⁸ These studies suggest that early insulin initiation may alter the progressive course of diabetes. This may be due to protection of, and possibly restoration of, beta-cell function. A patient who achieves restoration of beta-cell function ('clinical remission') can then be maintained on diet, weight control and exercise.

Concern about weight gain and fear of hypoglycaemia are major barriers in initiating insulin therapy. A variety of insulin analogues are now available with lower risk of hypoglycaemia and resulting in less weight gain.^{19–23} New insulin analogues more closely mimic the kinetic profile of endogenous insulin and allow for flexible dosing in pen devices that are generally well received by patients.



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Despite available evidence there appears to be 'psychological insulin resistance' not only from patients, but also and perhaps more importantly from physicians in initiating insulin. Benefits of early insulin therapy need to be conveyed to both patients and health care professionals through targeted education. Type 2 diabetes patients treated with insulin have been shown to have similar levels of motivation to comply with treatment compared with those not started on insulin. Once the patients have accepted insulin treatment the stress of treatment seemed less severe than expected.²⁴ Combining use of modern insulins with improvements in patient education should help facilitate early initiation of insulin and make insulin starts simpler and easier to adopt.

Summary

In summary, aggressive and often temporary use of insulin therapy at the outset of diagnosis of type 2 diabetes may alter the progressive course of diabetes by

protecting, and possibly restoring, beta-cell function. With the availability of insulin analogues, effective glycaemic control can be achieved with minimal weight gain and hypoglycaemia. Achieving and maintaining tight glycaemic control early are the primary goals of therapy which is the key element in preventing the incidence and progression of vascular complications, translating into improved overall health with decreased co-morbidities and reduced health care costs.

Declaration of interest

Dr Kong has received speakers' honoraria and travel support to attend academic meetings from Lilly Diabetes Care, Novo Nordisk Pharmaceuticals, Sanofi-Aventis, Astra Zeneca, MSD and Takeda.

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References are available online at www.practicaldiabetesinternational.com.

AGAINST

Dr Alex Bickerton

Consultant Physician, Yeovil District Hospital NHS Foundation Trust, UK

The modern diabetologist is faced with an increasingly bewildering array of therapeutic options for the management of patients with type 2 diabetes. There is no shortage of guidance from august organisations advising where to use which agent.¹⁻³ Although the algorithms offered are complex and open to interpretation, none advises insulin at diagnosis. This is for good reason and I would strongly argue that, for the vast majority of patients, insulin should be the very last of the list of potential initial treatments.

When considering therapeutic options in any medical condition, but particularly in the field of diabetes, there are a number of closely inter-related questions that influence the decision making process:

- What is the proposed treatment trying to achieve?
- Is the treatment likely to work?
- What are the potential disadvantages or side effects of the proposed treatment?
- And most important of all: what does the patient want?

What is the proposed treatment aiming to achieve and is it likely to work?

Broadly, the aims of management in patients with type 2 diabetes are to improve quality of life and reduce complications. The UKPDS⁴ and more recently the ADVANCE⁵ and ACCORD⁶ studies have clearly demonstrated that intensive blood glucose control significantly reduces the risk of microvascular complications. Although controversy remains over the role of glycaemic control in macrovascular disease, the UKPDS legacy data are certainly compelling.⁷

There is no doubt that insulin *will* achieve targets set for blood glucose control,⁸ prompting the argument for insulin as initial therapy. However, the risk reduction in

microvascular endpoints between study groups is related to differences in glycaemic control rather than the agent used to achieve this.⁴ Thus, the endpoint evidence does not support the use of insulin *per se*. The next obvious question is: does insulin address the underlying pathophysiology of diabetes? If so, then it would seem logical to choose insulin from among the options available to achieve glycaemic targets. Type 2 diabetes is traditionally thought of as being due to a mixture of insulin resistance and beta-cell failure. However, it is now clear that not only are the pancreas, liver and muscle involved in glucose homeostasis, but so too are adipose tissue, the gastrointestinal tract, the kidney and the brain.⁹ Insulin's actions on these organs are complex. Pragmatic studies of the use of insulin to improve glucose metabolism, and specifically beta-cell function, in patients newly diagnosed with type 2 diabetes have not demonstrated any advantage of insulin over sulphonylureas.^{10,11} Thus, analogous to the clinical endpoint studies, it is glycaemic control itself rather than the agent used that improves glucose metabolism. Therefore, exogenous insulin will effectively replace a deficiency of pancreatic production but, in contrast to the thiazolidinediones^{12,13} and incretins,^{14,15} will have no effect on the complex multi-organ pathophysiological processes that underlie type 2 diabetes.

What are the potential disadvantages or side effects of the proposed treatment?

Undoubtedly, the greatest fear related to insulin therapy, shared by physicians and patients alike, is that of hypoglycaemia. The received wisdom is that the frequency of hypoglycaemia in patients with type 2 diabetes is lower than in those with type 1 diabetes. This is undoubtedly true if considering all patients with type 2 diabetes.^{16,17} However, this does not mean that the problem is trivial. In the UKPDS the mean proportion of patients per year experiencing any hypoglycaemic event was 36.5% in those taking insulin, while the proportion experiencing a major hypoglycaemic event was 2.3%. This compares to



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rates of 11–17.7% and 0.4–0.6% respectively in those taking sulphonylureas.⁴ Furthermore, longer-term observational data suggest that the rate of hypoglycaemia in patients with type 2 diabetes *on insulin* is very similar to that of patients with type 1 diabetes.¹⁸ Indeed, duration of diabetes profoundly influences the risk. In a cohort of patients diagnosed with type 2 diabetes for 10 years, 15% of subjects experienced a major hypoglycaemic episode during the preceding year. The frequency of severe hypoglycaemia increased with age, duration of diabetes and duration of insulin therapy.¹⁹ Therefore, initiating insulin at diagnosis would very significantly increase the risk of hypoglycaemic events with the associated personal costs to the individual, in terms of disrupted lifestyle and loss of confidence, as well as economic costs to society, in terms of ambulance and hospital care.^{18,20}

Second only to the concerns regarding hypoglycaemia are those of weight gain. Studies of the use of insulin in patients with type 2 diabetes have universally demonstrated weight gain, ranging between 1.9kg²¹ and 8.7kg.²² Aside from the cosmetic implications, weight gain is of especial concern due to the association with cardiovascular risk. An increased BMI is associated with hypertension, dyslipidaemia and inflammation.²³ Furthermore, the DECODE study group have demonstrated that these risk factors, when taken together in the guise of the metabolic syndrome, translate into increased cardiovascular mortality.²⁴ Thus, at diagnosis of type 2 diabetes, it seems entirely counterintuitive to enthusiastically advocate weight *loss* through lifestyle changes while simultaneously commencing insulin, which will undoubtedly induce weight *gain*.

What does the patient want?

At present, insulin is only available in the UK as a subcutaneous injection. This is, at best, inconvenient and, at worst, associated with such psychological distress that insulin therapy is nigh on impossible. Such needle phobia is relatively rare;²⁵ however, it is self-evident that given the practical disadvantages, patients are unlikely to select insulin from the range of initial treatments available for type 2 diabetes. Furthermore, although weight gain and hypoglycaemia are important, there are

a number of psychosocial effects of commencing insulin that must equally not be forgotten or underestimated. Firstly, there is the danger of giving a message of physician expectation of patient failure by overtly suggesting that patients would never have managed to make the lifestyle changes advocated. Secondly, initiating insulin at diagnosis of type 2 diabetes immediately undermines the importance of lifestyle measures, suggesting that diet and physical activity are not really important as insulin will solve the problem. Finally, there are significant social implications of taking insulin including choice of occupation, the cost and availability of all forms of insurance and the practical considerations around travel. Unfortunately, there is a dearth of high quality data in this field. However, Polonsky *et al.* clearly showed that patients' negative attitudes toward insulin were common and particular concerns regarding insulin initiation included personal failure, low self-efficacy and restrictiveness.²⁶

Conclusion

Therefore, in answer to the questions set out at the start, I would argue that, as an initial therapy, insulin may achieve a target number but is fraught with disadvantage, will not address the disease processes and will certainly be far from what the patient wants. Lifestyle changes are the cornerstone of the management and should remain initial therapy for all but the rarest patients with type 2 diabetes. Hippocrates tells us to 'First do no harm'. As diabetologists, we pride ourselves on listening to our patients. By prescribing insulin at the outset of diagnosis of type 2 diabetes it is likely that we will do harm and we are certainly not listening to our patients.

Declaration of interest

Dr Bickerton has given talks sponsored by: Eli Lilly, Novo Nordisk, GlaxoSmithKline, Takeda, Bristol-Myers Squibb, Astra Zeneca and Merck.

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References are available online at www.practicaldiabetesinternational.com.



Online resource

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Dr Alex Bickerton

Consultant Physician, Yeovil District Hospital NHS Foundation Trust, UK

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