Initiating Insulin in Type 2 Diabetes Mellitus: There's no Rush

Yossi Cohen MD

Diabetes Clinic, Maccabi Health Services, Israel

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Type 2 diabetes mellitus has become an epidemic in the past several decades due to the advancing age of the population, increased prevalence of obesity and decreased physical activity – all associated with a western lifestyle [1]. In fact, 70% of patients with type 2 diabetes die of cardiovascular disease [2–4]. Today, diabetes contributes to more cases of adult-onset loss of vision, renal failure and amputation than any other disease [5].

The traditional approach for the treatment of type 2 diabetes is stepwise: starting with diet and exercise, followed by a mono-oral hypoglycemic drug, and later a combination of OHD with up to four types of drugs. Insulin therapy either in combination with OHD or as monotherapy has generally been recommended for patients with long duration of the disease, usually more than 10 years from diagnosis, by which time most of these patients already suffer from diabetic complications [5–8]. Insulin is the oldest of the hypoglycemic agents. Not only is it the only one that occurs naturally in humans, but it also has no upper dose limit. Numerous studies have demonstrated that near-normal glycemic levels are achievable when adequate doses of insulin are used [9–11]. Despite these advantages, insulin therapy is still considered by many physicians to be indicated only in cases with long duration of diabetes and failure of long-term maximal doses of OHD.

Barriers to early insulin treatment in type 2 diabetes

Some of the barriers derive from physicians' fears that insulin therapy carries the additional risks of hypoglycemia and weight gain. Moreover, many feel that data on the benefits of insulin therapy in preventing late micro- and macrovascular complications are insufficient. Consequently, many primary physicians are reluctant to initiate insulin therapy in their clinics. Other major limitations in initiating insulin therapy are the fears of the patients themselves. Patients fear injecting drugs, and they worry about their inability to conduct a normal social life at work, school, during travel, etc. In addition, there is the misconception in society that insulin-treated people have a more serious disease than people who receive pills.

Can early insulin therapy change the natural course of the disease?

Glycemia deteriorates progressively the longer diabetes is present, presumably as a result of decreasing beta-cell function. Some studies demonstrated that early intervention with intensive insulin therapy in newly diagnosed type 2 diabetes restores the endogenous insulin secretion, characterized by normoglycemia and no need for hypoglycemic medications. However, the long- term effect of this intervention is unknown [10,11].

There are insufficient data indicating that any of the hypoglycemic treatment regimens is specifically better in preventing late microvascular or macrovscular diabetes complications [12]. The ORIGIN study (Outcome Reduction with Initial Glargine Intervention) has enrolled patients with early diabetes, impaired fasting glucose, or impaired glucose tolerance, and with coexisting cardiovascular disease. This study, only recently initiated, was designed to compare early insulin therapy versus standard care in order to determine whether this treatment in early diabetes and in the pre-diabetic state will prevent or reduce the incidence of cardiovascular events and progression of the disease.

Intensive insulin therapy has proven superior in critically ill patients. Intensive insulin therapy was shown to improve the prognosis in post-myocardial infarction patients with type 2 diabetes [13], and by maintaining blood glucose at or below 110 mg/dl reduces morbidity and mortality among critically ill patients in the intensive care unit [14].

How acceptable is insulin in diabetic patients?

The UKPDS (United Kingdom Prospective Diabetes Study) demonstrated that insulin therapy results in more weight gain than

OHD = mono-oral hypoglycemic drug

sulfonylurea, with an average difference of 2 kg. Metformin treatment was associated with the least weight gain [12], while limited experience with thiazolidinediones showed that their use is associated with considerable weight gain [15].

Insulin treatment can lead to hypoglycemia, and in order to avoid this complication patients are instructed to eat often and not to skip a meal. Moreover, the introduction of both new recombinant short-acting insulin analogs with more physiologic properties and long-acting peakless analogs provides the means to achieve good glycemic control with reduced risk of severe hypoglycemic episodes [16]. In addition, the development of painless and continuous systems for glucose monitoring improves patients' adherence and the effectiveness of intensive insulin therapy. The availability of insulin injection devices like insulin pens and continuous insulin infusion systems offers the patient convenience and flexibility.

When is the appropriate time to start insulin therapy?

Sulfonylurea and metformin treatment is sufficient for a limited duration of time in many patients, and most patients require a change or the addition of other medications after less than 5 years [17]. Unfortunately, too many diabetic patients do not achieve the therapeutic targets of glycemic control with maximal doses of OHD. Delaying insulin therapy is usually due to hesitation and unwillingness of both physicians and patients.

Every diabetic patient who fails to achieve with treatment the well-established metabolic goals [18] – fasting blood glucose <130 mg/dl, post-prandial glucose levels <150 mg/dl, and glycosylated hemoglobin <7% – is a candidate for insulin therapy. In patients who are managed with diet and physical activity and fail to achieve these goals after a short period (3–4 months), metformin therapy can be considered [17]. Failure to achieve good control, mainly of fasting blood glucose, necessitates the addition of long-acting insulin at bedtime [16,19]. In patients who fail to achieve the post-prandial glycemic goals, short-acting insulin with every meal can be considered as an alternative to sulfonylurea or glitinides and/or alpha-glucosidase inhibitors [20]. In Europe and Israel, thiazilidendiones are not recommended as first-line therapy, and before adding these drugs one must evaluate their effectiveness for glucose control versus the cost of weight gain [21]. For patients unable to inject insulin or to perform self-monitoring of blood glucose due to motor or cognitive incapacities, special consideration is needed.

Conclusions

Insulin therapy has a major role in the treatment of type 2 diabetes. The usual slow transition from one regimen of therapy with OHD to the next, without achieving adequate control, should be avoided. Continued attention to lifestyle modification should be encouraged at every step of diabetes intervention. Data on the role of insulin therapy in the early stages of diabetes and in the pre-diabetic state in changing the progression of the disease are still insufficient and more long-term studies are needed. Critically ill patients and patients with acute myocardial infarction may benefit from intensive insulin therapy.

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Correspondence: Dr. Y. Cohen, Diabetes Clinic, Maccabi Health Services, Israel.
email: josefcohen@hotmail.co.il