Early Insulinization to Prevent Diabetes Progression

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This article reviews data collected from clinical studies regarding the place of early insulin treatment in preservation of β-cell function in type 2 diabetic patients. It emphasizes the stepwise progression of the data, starting with small uncontrolled studies and progressing to larger-scale controlled studies. It summarizes current knowledge in the field, emphasizing the additional information gained from the Outcome Reduction with Initial Glargine Intervention (ORIGIN) trial (1).

Effect of glucotoxicity and lipotoxicity on β-cells

Glucotoxicity and lipotoxicity have long been recognized as having a deleterious effect on both β-cell function and insulin action (2–4). Glucolipotoxicity refers to the combined deleterious effects of elevated glucose and free fatty acids on β-cell mass and function (5). Significant progress has been made in recent years toward a better understanding of the cellular and molecular basis of glucolipotoxicity (5–7). Insulin protects the β-cell by inducing rapid reversal of glucolipotoxicity and β-cell rest (8,9). The rapid reversal of glucolipotoxicity by insulin therapy is one of the justifications for early insulin treatment (2–10).

Treat to target or treat to failure?

The importance of avoiding prolonged hyperglycemia in patients with short diabetes duration in order to minimize its negative effect on late microvascular and macrovascular complications has been established (11). Hence, present guidelines (12–16) recommend early initiation of life style changes with or without metformin and subsequent addition of 2nd- and 3rd-line therapy when previous treatments fail to achieve or maintain the goal. The goals in the treatment of hyperglycemia in newly diagnosed type 2 diabetes are to achieve near-normal glucose control as early as possible in order to preserve β-cell function and maintain long-term normoglycemia.

The capacity of antidiabetes medication to maintain prolonged glycemic control (glucose durability) is of great importance. In the ADOPT study, rosiglitazone (17) demonstrated the best "glucose durability" compared with sulfonylurea (SU) and metformin. Glucagon-like peptide (GLP)-1 analogs were shown to have a potential β-cell–protective effect (18,19). In this article, we will focus on the protective effect of insulin on β-cells compared with those of oral antidiabetes drugs (OADs).

Milestones in clinical research of early insulinization for preservation of β-cell function

Correction of hyperglycemia with insulin increases peripheral sensitivity and improves residual β-cell function (20). The hypothesis of β-cell protection by early insulin therapy was tested by several clinical studies, beginning with noncontrolled studies in patients with severe hyperglycemia and followed by randomized controlled studies in severely uncontrolled newly diagnosed patients using short-term and longer-term insulin therapy as well as well-controlled type 2 diabetic patients using long-term insulin therapy (Fig. 1 and Table 1).

Early noncontrolled studies in severe hyperglycemic patients

In 1997, Ilkova et al. (21) published their study of 13 patients with extremely high glucose levels (average HbA$_{1c}$ 11.0%) who were treated with insulin pump–subcutaneous insulin infusion (SCII) for 2 weeks. Twelve of the 13 patients achieved glucose control, and 6 maintained their glucose control for a year without necessitating any further antidiabetes drug (ADD) treatment. This small uncontrolled study may be viewed as a feasibility test for the studies that followed.

The study of Park and Choi (22) included 91 Korean type 2 diabetic patients with average diabetes duration of 7.2 ± 4.9 years. Patients' diabetes was not well controlled on lifestyle (51.7%), OAD (27.5%), insulin (12.3%), or combination therapy (5.8%), and patients were switched to SCII therapy. Remission rate was higher in patients with short diabetes duration (3.3 ± 2.7 years), lower postprandial glucose levels, and higher BMI and without diabetes complications. This study, however, included patients with long diabetes duration.
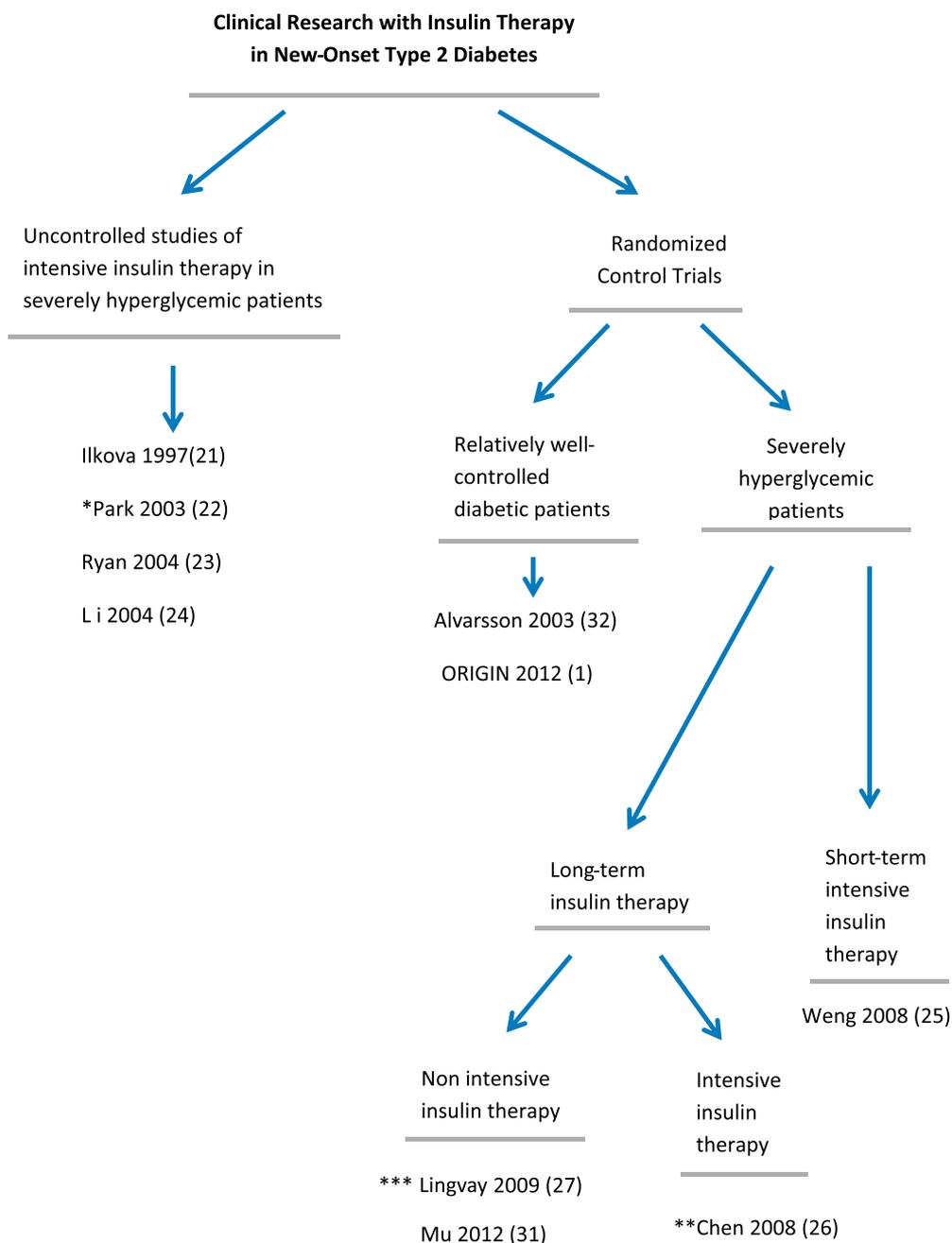
Ryan, Imes, and Wallace (23) studied 16 drug naïve, newly diagnosed type 2 diabetic patients with fasting plasma glucose (FPG) levels >11.0 mmol/L in order to define which patients would respond to short (2–3 weeks) intensive insulin therapy. End point was prolonged remission, defined as no need for ADD treatment after 1 year of follow-up. After 1 year, seven patients did not require ADD. These patients required less insulin during the active insulin therapy phase (0.37 ± 0.05 vs. 0.73 ± 0.07 units/kg/day) and had lower FPG at the end of the insulin therapy period (5.9 ± 0.3 vs. 7.7 ± 0.4 mmol/L). This was a noncontrolled study with a small number of patients planned to identify the patients who will most likely respond best to early insulin intervention. Its design and size require repetition for validation of its conclusions.

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**Clinical Research with Insulin Therapy
in New-Onset Type 2 Diabetes**

Uncontrolled studies of intensive insulin therapy in severely hyperglycemic patients

Randomized Control Trials

Ilkova 1997(21)

*Park 2003 (22)

Ryan 2004 (23)

L i 2004 (24)

Relatively well-controlled diabetic patients

Severely hyperglycemic patients

Alvarsson 2003 (32)

ORIGIN 2012 (1)

Long-term insulin therapy

Short-term intensive insulin therapy

Weng 2008 (25)

Non intensive insulin therapy

Intensive insulin therapy

*** Lingvay 2009 (27)

Mu 2012 (31)

**Chen 2008 (26)

*Not only newly diagnosed type 2 diabetes

** Both groups received short-term intensive insulin therapy

*** Both groups were treated for 3 months with Premix insulin analogs

Figure 1—*Milestones in clinical research of early insulin therapy.*

An important larger uncontrolled study by Li et al. (24) enrolled 138 newly diagnosed type 2 diabetic patients with FPG >11.1 mmol/L. Patients were hospitalized and treated for 2 weeks with continuous subcutaneous insulin infusion (CSII). Optimal glycemic control was achieved in 126 patients within 6.3 ± 3.9 days. Insulin therapy was stopped,

Table 1—Summary of the baseline characteristics, intervention, and outcomes in the studies presented in the article

Ref.	N patients/ ± Asian population	Mean fasting glucose (mg/dL) and/or HbA$_{1c}$ at baseline (%)	Intervention	Duration of intervention	% or ratio of achievement of glycemic control and days to glycemic control	% or ratio of responders at 12 months
Noncontrolled, intensive treatment in small groups of severely hyperglycemic patients						
Ilkova et al., 1997 (21)	13/–	218 mg/dL, 11%	CSII	2 weeks	12/13	6/13
Park et al., 2003 (22)	91/+	13.2%	CSII	2–8 weeks	34%	31%
Ryan et al., 2004 (23)	16/–	239 mg/dL, 11.8%	Basal bolus	2–3 weeks	16/16 within 2–3 weeks	7/16
Li et al., 2004 (24)	138/+	245 mg/dL, 10.1%	CSII	2 weeks	126/138 within 6.3 ± 3.9 days	47% of 68 patients who were followed
Controlled studies of intensive insulin treatment in groups of severely hyperglycemic patients						
Chen et al., 2008 (26)	44 (30 analyzed)/+	11.9 vs. 11.3%	Intensive insulin therapy	10–14 days. 25 continued insulin for 6 months and 19 continued OAD (metformin ± glicazide). Only 30 with HbA$_{1c}$ <7% analyzed	At 6 months, HbA$_{1c}$ <7% achieved in 22/25 of the insulin-treated group, 8/19 of the OAD-treated group	NA
Weng et al., 2008 (25)	382/+	11.2 ± 3.1%; CSII 9.8 ± 2.3%, MDI 9.7 ± 2.3%, OAD 9.5 ± 2.5%	CSII vs. MDI vs. oral (BMI 20–25 kg/m^2 glicazide; 25–35 kg/m^2 metformin, combination if needed)	2 weeks after normoglycemia: FPG <6.1 mmol/L, 2HPP <8.0 mmol/L achieved	CSII 97.1% in 4.0 ± 2.5 days, MDI 95.2% in 5.6 ± 3.8 days, and OAD 83.5% in 9.3 ± 5.3 days	CSII 51.1%, MDI 44.9%, OAD 26.7%; P = 0.0012
Controlled studies with nonintensive insulin therapy in severely hyperglycemic patients						
Lingvay et al., 2009 (27)	58/–	After 3-month treatment with insulin + metformin 6.0 ± 0.5 vs. 5.9 ± 0.5% in groups randomized to insulin vs. oral	After 3-month treatment with insulin + metformin: insulin with metformin vs. metformin + pioglitazone + glyburide	83% of patients in the insulin group and 72% of patients in the oral group completed the 3-year study	NA	Among completers, HbA$_{1c}$ 6.1 ± 0.6 vs. 6.0 ± 0.8% in insulin vs. oral-treated group

Table 1—Continued

Ref.	N patients/ ± Asian population	Mean fasting glucose (mg/dL) and/or HbA$_{1c}$ at baseline (%)	Intervention	Duration of intervention	% or ratio of achievement of glycemic control and days to glycemic control	% or ratio of responders at 12 months
Mu et al., 2012 (31)	129/+	13.30 ± 2.1 vs. 13.49 ± 2.22% in OAD + insulin vs. OAD	Insulin glargine and OAD vs. OAD	3 months after normoglycemia was achieved	98.3% within 10.4 ± 2.5 days vs. 95.7% within 12.4 ± 3.4 days in insulin + OAD vs. OAD	Maintained glycemic control without need for further treatment: insulin + OAD 37.9% vs. OAD 20.9%
Early insulin treatment in relatively well-controlled patients						
Alvarsson et al., 2003 (32)	39/–	6.9 ± 0.2 vs. 7.3 ± 0.4% in insulin vs. glibenclamide	Premix insulin vs. glibenclamide	2 years	NA	At 1 year, glucagon-stimulated C-peptide increased in insulin-treated and decreased in glibenclamide group
ORIGIN, 2012 (1)	12,537/–	124 mg/dL (IQR 108–148), 6.4% (IQR 5.8–7.2)	Insulin glargine titer to FPG <95 mg/dL vs. standard of care	6.2 years (IQR 5.8–6.7)	NA	NA

2HPP, 2 h postprandial.

and patients were instructed to continue with lifestyle treatment. The percentage of patients who maintained near-normal glucose control defined as FPG <6.1 mmol/L and postprandial glucose <8.0 mmol/L for 3, 6, 12, and 24 months was 72.6, 67.0, 47.1, and 42.3%, respectively. Homeostasis model assessment (HOMA) of β-cell function (HOMA-B) and the area under the curve (AUC) of insulin during intravenous glucose tolerance test were higher in the remission group (145.4 ± 89.6 vs. 78.5 ± 68.5 pmol/L/min, P = 0.002, and 1,423.4 ± 523.2 vs. 1,159.5 ± 476.8 pmol/L/min, P = 0.044). The conclusion of this study was that short-term insulin therapy can induce long-term glycemic control in newly diagnosed type 2 diabetic patients with severe hyperglycemia. The main limitations of this study were the lack of a control group and the exclusion from the analysis of 12 patients who failed to achieve glycemic control after 2 weeks' CSII treatment.

Randomized controlled studies in new-onset diabetic patients
The results of the previously listed uncontrolled studies were reconfirmed and strengthened by a series of controlled studies. The controlled studies are divided into studies done in severely hyperglycemic patients versus relatively well-controlled patients. The studies done in severely hyperglycemic patients can be further divided into studies with long versus short insulin therapy with intensive insulin treatment in some and less intensive therapy in others.

Randomized controlled studies of short-term insulin intervention in new-onset severely hyperglycemic patients
The first large, multicenter, controlled trial (25) randomized 382 patients from nine different centers in China. The patient population included newly diagnosed type 2 diabetic patients with FPG of 7.0–16.7 mmol/L. The patients were randomly assigned to insulin treatment with multiple daily injections (MDI) or SCII or to treatment with OAD. The type of OAD was given according to BMI: patients with BMI 20–25 kg/m^2 were treated with gliclazide, while patients with BMI 25–35 kg/m^2 were treated with metformin; combination therapy of these drugs was given if needed. Glycemic control was achieved faster and in a higher percentage of the patients in the insulin-treated arms compared with the

OAD group/arm (97.1% of the patients in the CSII group achieved glucose control within 4.0 ± 2.5 days vs. 95.2% within 5.6 ± 3.8 days in the MDI group and 83.5% within 9.3 ± 5.3 days in the OAD group). Two weeks after glycemic control was achieved, antidiabetes treatment was stopped. A year later, the target glycemic control in the insulin-treated groups was maintained in a significantly higher percentage of patients (51.1, 44.9, and 26.7% in the CSII, MDI, and OAD groups, respectively; $P = 0.0012$). β-Cell function was measured by HOMA-B and acute insulin secretion during the first 10 min after intravenous glucose tolerance test. Both HOMA-B and acute insulin response improved significantly after intensive interventions. The increase in acute insulin response was sustained in the insulin groups but significantly declined in the oral hypoglycemic agents group at 1 year in all patients in the remission group. There are two main limitations to this study: the use of SU in the control group, which limited the ability to separate the protective effect of insulin therapy on β-cell function, from the possible negative effect of SU. This limitation is repeated in other studies that involved treatment with SU in the control group (25–27). The second limitation is its external validity to the non-Asian population. This limitation is also repeated in many other studies (22,24,26).

A recent systematic review and meta-analysis (28) of short-term intensive insulin therapy in type 2 diabetes included the results from seven studies (five of them uncontrolled) ($n = 839$ participants). The meta-analysis demonstrated an increase in HOMA-B (1.13 [95% CI 1.02–1.25]) and decrease in HOMA of insulin resistance (-0.57 [-0.84 to -0.29]) compared with baseline after short-term intensive insulin therapy. Four of the studies reported glucose remission rates: 66.2, 58.9, 46.3, and 42.1% at 3, 6, 12, and 24 months, respectively. The authors concluded that short-term intensive insulin therapy might modify the natural history of diabetes.

Randomized controlled studies of long-term intensive insulin intervention in new-onset severely hyperglycemic patients
A controlled, single-center study (26) tested the results of prolonged therapy with multiple daily insulin injection (MDII) versus OAD after initial intensive insulin therapy in newly diagnosed diabetic patients. Fifty newly diagnosed type 2 diabetic patients with severe hyperglycemia (defined as FPG >300 mg/dL or random glucose >400 mg/dL) were hospitalized for 10–14 days and treated with MDII. Patients were then randomized to continue insulin therapy ($n = 25$), or to switch to OAD (metformin or gliclazide) ($n = 19$). Both groups were followed closely, and their treatment was titrated to preset glycemic goals. The insulin-treated group was better controlled both at 6 months (HbA$_{1c}$ 6.33 ± 0.70 vs. 7.50 ± 1.50%; $P = 0.002$) and at 1-year follow-up (6.78 ± 1.21 vs. 7.84 ± 1.74%; $P = 0.009$). Patients who achieved Hba$_{1c}$ <7% were tested for β-cell function using oral glucose tolerance test (OGTT) at baseline and after 6 months: 22 of 25 in the insulin-treated group and 8 of 19 in the OAD-treated group. There was a significant improvement in both groups in glucose AUC during OGTT. HOMA-B and insulin AUC during OGTT were improved significantly only under insulin therapy. The authors concluded that 6 months' treatment with insulin was better for both glycemic control and preservation of β-cell function in new-onset diabetic patients with severe hyperglycemia. This conclusion, however, is debatable, since it was drawn from a small group that included only the responders and given that the performance of OGTT in the entire study population is missing. Other limitations of this study are its homogenous Asian population, which may decrease external validity to other populations, and the use of SU in the control group. The effect on HOMA-B and on insulin secretion during OGTT might be attributed to the positive effect of insulin on β-cell rest or to the negative effect of SU due to overfunction of β-cell.

Randomized controlled studies of long-term nonintensive insulin intervention in new-onset severely hyperglycemic patients
Lingvay et al. (27) studied the effect of long-term insulin therapy with premix insulin analog twice daily (in combination with metformin) versus a combination of three OADs. Patients were recruited in a single center and were newly diagnosed and drug naïve. They were enrolled in a lead-in period of 3 months during which time they were treated with premix insulin analog (premix insulin aspart 30/70) and metformin and achieved glycemic control, with reduction of HbA$_{1c}$ from 10.8 to 5.9% (29). After completion of the lead-in period, they were randomized to continue insulin-based therapy (29 patients) or to treatment with triple oral therapy: metformin, pioglitazone, and glyburide (29 patients). Eighty-three percent of patients in the insulin group and 72% of patients in the triple oral treatment group completed the 3-year study. Analysis was done on this group and not on the intention-to-treat group. Glycemic control was very well maintained throughout the 3 years in both groups: HbA$_{1c}$ was 6.1 ± 0.6% in the insulin group vs. 6.0 ± 0.8% in the triple oral therapy group ($P = 0.26$). Weight gain was demonstrated in both groups: 7.2 kg (95% CI 4.2–10.1) and 4.5 kg (0.9–8.0) ($P = 0.09$) in the oral and insulin-treated groups respectively. The incidences of mild and severe hypoglycemia events were similar in both groups. There were also no differences between the groups regarding compliance or satisfaction with the treatment as well as quality of life as measured by the modified Diabetes Quality of Life Clinical Trial Questionnaire. The conclusion of this study is that prolonged insulin treatment is as effective, safe, and well accepted for new-onset type 2 diabetic patients as triple drug therapy. Another analysis of the same study, which was extended from 36 to 42 months, was published by Harrison et al. (30). β-Cell function was assessed using the results of mixed-meal tolerance test at randomization and at 6, 12, 18, 30, and 42 months. At 3.5 years, both groups had well-preserved β-cell function with no significant change from baseline or within the two groups, as measured by AUC of C-peptide ($P = 0.14$) or C-peptide to glucose AUC ($P = 0.7$) during mixed-meal tolerance test. The conclusion of this study was that β-cell function can be preserved in new-onset type 2 diabetic patients for at least 3.5 years by intensive glucose control with either insulin-based therapy or triple drug therapy including peroxisome proliferator–activated receptor-γ.

There are several limitations to this study (27,29,30): dropout rates were high and unequal (17 and 28% in the insulin and triple OAD groups respectively), the initial 3 months' intensive insulin therapy period might have influenced the results, and the combined triple OAD therapy does not allow distinction among different drugs' effects on β-cell function. On the other hand, the long-term follow up and the diverse ethnic backgrounds (43% African American, 17% white, and 38% Hispanic) are important strengths of this study.

While earlier studies used intensive insulin treatment with MDII or SCII, a more recent study was conducted in order to determine whether basal insulin can achieve a similar effect. Mu et al. (31) enrolled 129 newly diagnosed type 2 diabetic patients with HbA_{1c} >9% and FPG >9 mmol/L. Patients were randomly divided to receive either OAD alone (glimepiride or metformin) or a combination of OAD and basal insulin (glargine). Treatment was stopped 3 months after normoglycemia was achieved, and patients were followed-up for a year. At 1 year follow-up, a higher percentage of the patients in the insulin plus OAD group maintained target glycemic control without need for further treatment (37.9%) compared with OAD only (20.9%). Both treatment groups had similar improvements in HOMA-IR (P = 0.23) while there was significantly greater improvement of HOMA-B in the insulin plus OAD group (2.17 ± 0.14 vs. 2.11 ± 0.13; P = 0.03). The difference in diabetes remission rates between the insulin plus OAD and the OAD groups in this study was lower than in previous studies (24–26). There are several possible contributing factors for this smaller effect: the use of basal insulin regimen instead of the more complicated MDII or CSII in previous studies, longer time to achieve glucose control in this study, and the use of a different SU (glimepiride instead of gliclazide). More studies in different populations are needed to confirm this finding.

Randomized control study in relatively well-controlled diabetes

The studies described above demonstrated that early insulin therapy in patients with new-onset uncontrolled, severely hyperglycemic type 2 diabetes may restore β-cell function and induce diabetic remission in a large percentage of patients. Can these results be generalized also to patients with relatively well-controlled diabetes?

The first randomized controlled study in relatively well-controlled new-onset diabetic patients was conducted by Alvarsson et al. (32). In this multicenter Swedish study, 39 newly diagnosed (0–2 years) type 2 diabetic patients were randomized to receive either two injections of premix insulin per day or glibenclamide for 2 years. β-Cell function, glucose control, and measurement of quality of life were measured. After 1 year, the glucagon-stimulated C-peptide was increased in the insulin-treated group and

decreased in the glibenclamide-treated group (P < 0.02). After 2 years, HbA_{1c} was increased in the glibenclamide group and stable in the insulin-treated group (P < 0.02). The effect on stimulated C-peptide might be attributed to the positive effect of insulin on β-cell rest or to the negative effect of SU due to overfunction of β-cell.

The ORIGIN Trial was planned, designed, and carried out in order to investigate whether early insulin therapy in high–cardiovascular risk patients with diabetes or prediabetes would reduce long-term cardiovascular events (1). This study added important knowledge on the effect of early insulin therapy in diabetic and prediabetic patients. The innovation of the ORIGIN study over previously mentioned studies was its size (12,537 subjects), duration (median follow-up 6.2 years), and inclusion of a diverse population (including prediabetes and well-controlled diabetic patients). Among the 1,456 nondiabetic patients included in the study, in the glargine-treated group compared with the standard-care group there was a 28% reduction in the risk of developing diabetes, as diagnosed by OGTT (odds ratio 0.72 [95% CI 0.58–0.91], P = 0.006) at study end. In a second OGTT done at a median of 100 days (interquartile range [IQR] 95–112) after insulin was discontinued, additional cases of diabetes were detected in both groups. The incidence of diabetes, however, was reduced in the patients previously treated with insulin (i.e., 30 vs. 35%; odds ratio 0.80 [95% CI 0.64–1.0]; P = 0.05). Another important aspect of this study was the high compliance of patients to insulin therapy: after 2 years, 5,398 participants in the insulin glargine group (90%) were adherent to insulin therapy; at 5 years, 4,719 (85%) were adherent. The intervention was insulin glargine titered to reach an FPG level ≤95 mg/dL. After 1 year, 50% of the insulin-glargine group had an FPG level of ≤95 mg/dL and up to 75% had FPG <108 mg/dL. This level of glucose control was maintained over a median follow-up of 6.2 years (IQR 5.8–6.7 years). The control group also had excellent glucose control, and the difference between the two groups was maintained at HbA_{1c} difference of 0.3% throughout the study.

It is interesting to note that most of the patients in the study achieved impressive glucose control even though they were not followed up in diabetology-specialized sites. These findings emphasize the relative

ease of glucose control with basal insulin in this group of patients. However, insulin therapy resulted in an increased incidence of hypoglycemic events. The incidence of a first episode of severe hypoglycemia was 1.00/100 person-years in the insulin glargine group and 0.31/100 person-years in the standard care group (P < 0.001). The incidence of any (i.e., confirmed or unconfirmed) nonsevere symptomatic hypoglycemia was 16.72 and 5.16/100 person-years, respectively (P < 0.001). Participants in the insulin glargine group gained a median of 1.6 kg (IQR −2.0 to 5.5), and participants in the standard care group lost a median of 0.5 kg (−4.3 to 3.2) during follow-up.

Identifying patients who are more likely to benefit from early insulin treatment

Defining which patients are more likely to respond to early insulin treatment is a complex but rewarding mission. A recent review by Retnakaran and Zinman (33) divided factors predicting the likelihood of sustaining prolonged euglycemia post–insulin treatment into three categories: factors at baseline, during the insulin treatment, and right after the insulin treatment. At baseline, some of the factors that may predict response are better glycemic control (22,25,28), higher BMI and insulin resistance (22,25,26,28), and shorter diabetes duration (22). Faster achievement of glucose control (25) and requirement of lower exogenous insulin doses during the insulin treatment (23), as well as better glycemic control (23–26) and greater improvement in β-cell function (24–26) immediately after insulin therapy, were all associated with higher remission rates. Patient attitude toward diabetes was another aspect that was found to be related to response rates to early insulin treatment (34). Patients who maintained diabetes remission after short CSII treatment (25) were more likely than those who did not to have higher scores in positive attitude, belief in importance of care, care ability, and self-care compliance scales.

Conclusions

When one considers initiation of insulin therapy in a type 2 diabetic patient with the intention to preserve β-cell function, the level of evidence supporting this decision is relatively high.

For the subgroup of patients with severe symptomatic hyperglycemia, there is strong evidence, in addition to guideline

recommendations (American Diabetes Association/ European Association for the Study of Diabetes, International Diabetes Federation, American Association of Clinical Endocrinologists, Canadian, and National Institute for Health and Care Excellence [12–16]), to support initiation of short-term insulin therapy. Insulin therapy is an effective way to reverse short-term glucotoxicity and lipotoxicity and shows evidence of midterm β-cell preservation. Short-term insulin treatment is safe, with low incidence of hypoglycemia (23–25) and less concern for weight gain. However, the best method for insulin treatment in such cases—basal insulin, premix insulin analogs, MDII, or CSII—and the length of insulin therapy should be further studied.

The place of long-term early insulin treatment in well-controlled type 2 diabetic patients is still debatable. Although the ORIGIN study demonstrated that early insulin therapy with insulin glargine is both safe and feasible, there are still the pros and cons of this treatment to consider. The benefits are as follows. 1) Insulin therapy can achieve near-normal FPG. 2) The achievement of such goals, especially in newly-onset diabetes, is relatively easy and can be maintained for many years. 3) Early treatment with insulin is safe with respect to both cardiovascular and tumor genesis. Among the drawbacks to consider regarding early insulin therapy are 1) weight gain (even though weight gain might be mild, its clinical consequences are yet unknown), 2) increased risk of hypoglycemia, and 3) patients' preference for different treatments.

In light of the above, who will be a good candidate for early insulin therapy? Beyond the consensus concerning severely hyperglycemic patients, other patients who may benefit from early insulin therapy may be those who have a more prominent increase in FPG compared with their increase in postprandial glucose. Another group may be the leaner type 2 diabetic patients, since increased weight is less of a risk, and they are more likely to be insulin deficient. Lastly, we may consider early insulin therapy in obese type 2 diabetes in combination with GLP-1 analogs or in patients treated with GLP-1 analog when FPG still remains high.

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