Insulin Therapy for Type 2 Diabetes

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A number of landmark randomized clinical trials established that insulin therapy reduces microvascular complications (1,2). In addition, recent follow-up data from the U.K. Prospective Diabetes Study (UKPDS) suggest that early insulin treatment also lowers macrovascular risk in type 2 diabetes (3). Whereas there is consensus on the need for insulin, controversy exists on how to initiate and intensify insulin therapy. The options for the practical implementation of insulin therapy are many. In this presentation, we will give an overview of the evidence on the various insulin regimens commonly used to treat type 2 diabetes.

Secondary analyses of the aforementioned landmark trials endeavored to establish a glycemic threshold value below which no complications would occur. The UKPDS found no evidence for such a threshold for A1C, but instead showed that better glycemic control was associated with reduced risks of complications over the whole glycemic range ("the lower the better") (4). For the management of type 2 diabetes, this resulted in the recommendation to "maintain glycemic levels as close to the nondiabetic range as possible" (5). However, in contrast to the UKPDS, the Kumamoto study observed a threshold, with no exacerbation of microvascular complications in patients with type 2 diabetes whose A1C was <6.5%, suggesting no additional benefit in lowering A1C below this level (2). Moreover, the intensive glycemia treatment arm of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, targeting A1C <6.0%, was discontinued because of higher mortality in this group compared with the standard therapy group targeting A1C from 7.0 to 7.9% (6). Therefore, the American Diabetes Association (ADA) recommendation of an A1C target <7.0% seems the most balanced compromise at present (7).

Another important conclusion of the UKPDS was that the risk reductions in long-term complications were related to the levels of glycemic control achieved, rather than to a specific glucose-lowering agent (1). This has left health care providers and patients with the difficult task of choosing from the wide variety of glucose-lowering interventions currently available. When considering the effectiveness, tolerability, and cost of the various diabetes treatments, insulin is not only the most potent, but also the most cost-effective intervention (8). Although insulin has no upper dose limit and numerous trials established that glycemic goals could be attained by using adequate insulin doses (5,8), in clinical practice, many patients have elevated A1C levels and experience years of uncontrolled hyperglycemia (9). Moreover, the Steno-2 Study demonstrated that only a minority of patients reached the intensive A1C target of <6.5%, compared with a far greater percentage of patients who reached the respective intensive treatment goals for blood pressure and serum lipid levels (10). Apparently, the initiation and intensification of insulin therapy is not as straightforward and simple as we had hoped. In accordance with the ADA and the European Association for the Study of Diabetes (EASD) (5,7), we advocate an algorithmic approach for the start and adjustment of insulin treatment, with modifications for individual patients as needed. This review contains an overview of the currently available insulin preparations and an outline of the merits and disadvantages of the various regimens commonly used for the initiation and intensification of insulin therapy in patients with type 2 diabetes. Our aim is to assist clinicians in designing individualized management plans for insulin therapy in type 2 diabetic patients.

HUMAN INSULIN AND ITS ANALOGS

— Insulin therapy with the conventional mealtime and basal insulin preparations has many shortcomings. First, the absorption of regular human insulin from the subcutaneous tissue is slow, and the metabolic action takes effect only 30–60 min after injection and peaks after 2–3 h. Consequently, treatment with regular insulin is associated with postmeal hyperglycemia and an increased risk of late-postprandial hypoglycemia. Second, the conventional basal NPH insulin has a distinct peak glucose-lowering effect, has a duration of action considerably shorter than 24 h, and is absorbed from the subcutaneous tissue at variable rates. These pharmacodynamic limitations predispose users to elevated glucose levels before breakfast and nocturnal hypoglycemia (11,12). To overcome these difficulties, insulin analogs with a modified amino acid sequence from the human insulin molecule were developed. The three rapid-acting analogs (aspart, glulisine, lispro) are absorbed more quickly than regular insulin because of reduced self-association. Their onset of action is within 15 min after subcutaneous injection, and they have a faster and greater peak action. Insulin glargine, the first long-acting insulin analog to reach the market, was initially proclaimed to have the ideal "peakless," nearly 24-h duration of action (13). However, these initial pharmacodynamic studies raised some criticism, and it should be concluded that there is no such thing as a "peakless" insulin preparation (12,14,15). Nevertheless, both long-acting insulin analogs (detemir and glargine) have a limited peak effect and a longer mean duration of action compared with NPH insulin (with glargine having a slightly longer action than detemir [13,16,17]).

It was expected that the rapid-acting and long-acting analogs, which more closely approximate physiological insulin secretion, would confer important clinical benefits (11). With respect to type 2 diabetes, the topic of this review, it is im-

portant to note that most patients with type 2 diabetes have residual endogenous insulin secretion in the context of insulin resistance. Therefore, the rationale for imitating the insulin secretion pattern of human physiology is less convincing than in type 1 diabetes. Indeed, in patients with type 2 diabetes, the rapid-acting analogs were not found to be superior to regular insulin in reducing A1C levels or rates of overall hypoglycemia (18). The clinical benefits of the long-acting insulin analogs compared with NPH insulin are limited to a reduction in (nocturnal) hypoglycemia (19).

WHEN SHOULD INSULIN THERAPY BE INITIATED? — Type

2 diabetes is a progressive disease, and thus, ultimately this question will arise for many of our patients. Unfortunately, there is no unequivocal answer, which was nicely illustrated by a recent interactive case vignette. The polling results demonstrated once again that the management of patients with type 2 diabetes uncontrolled by two oral glucose-lowering agents is controversial. Furthermore, the preferred treatment option was found to be related to the respondents' locations and self-reported specialties (20).

Traditionally, there has been a stepwise introduction of glucose-lowering interventions, with the final "step" of insulin therapy being administered 10–15 years after diagnosis (8). Both patients and physicians are often reluctant to start insulin because of fears of painful injections, hypoglycemia, and weight gain (21,22). Additional reasons for "psychological insulin resistance" among patients are negative beliefs about insulin treatment permanence, restrictiveness, low self-efficacy, personal failure, and illness severity (22). Drawback of the stepwise approach is that the introduction of successive interventions after treatment failure is often delayed, exposing patients to many years of uncontrolled hyperglycemia (9). Another reason for a more rapid response to treatment failure is that lowering glycemia has been shown to improve insulin resistance as well as endogenous insulin secretion (23). This was recently confirmed by Weng et al. (24) who found that a brief course of insulin therapy in subjects with newly diagnosed type 2 diabetes not only restored, but also maintained, β-cell function, resulting in prolonged glycemic remission. Interestingly, remission rates were significantly higher in the intensive

insulin groups than in the intensive oral therapy group. However, Weng's findings need to be confirmed, and also for reasons of practicality and patients' acceptance, we advocate stepwise diabetes treatment, provided that "an A1C of ≥7.0% serves as a call to action to initiate or change therapy" (5). Moreover, the response to this call should be swift; given the great (cost-) effectiveness, we advocate the initiation of insulin when glycemic goals are not attained after 2–3 months of maximally dosed dual oral therapy. For patients intolerant to one or more oral glucose-lowering agents and who do not achieve glycemic control with oral monotherapy, as well as those with a personal preference, earlier initiation of insulin is indicated. It is noteworthy that rapid addition of insulin therapy is supported by numerous studies showing improved treatment satisfaction and quality-of-life for type 2 diabetic patients who had started using insulin (25,26).

HOW SHOULD INSULIN THERAPY BE INITIATED?

Basal insulin
The "treat-to-target" clinical trials established that the addition of basal insulin to existing oral glucose-lowering therapy achieves good glycemic control in the majority of patients with type 2 diabetes (27–29). According to the ADA/EASD algorithm for the management of type 2 diabetes, insulin could be initiated with either once-daily NPH insulin or a long-acting insulin analog (5). For several reasons, we consider NPH insulin the preferred option. As previously mentioned, the relative benefit of the long-acting insulin analogs is limited to a reduction in (nocturnal) hypoglycemia (19). Moreover, this advantage is relevant to only a minority, since most patients with type 2 diabetes starting insulin therapy do not experience hypoglycemia at all (12). A recent meta-analysis that included six randomized comparisons of NPH and glargine found event rates for self-monitoring of blood glucose (SMBG) confirmed symptomatic hypoglycemia <65 mg/dl of only 138 and 91 events per 100 patient-years for these insulins, respectively, in insulin-naive type 2 diabetic patients who achieved an A1C of 7.0% (30). Finally, in this era of relentlessly increasing incidence rates for type 2 diabetes, physicians cannot afford to disregard the elevated cost of the newer insulin preparations. In the U.S., the average retail

price of a 10-ml vial of the long-acting insulin analogs is $105 compared with $53 for a vial of NPH insulin (31). In this respect, clinicians should realize that when they stop prescribing conventional insulin preparations, with established beneficial effects, they provide a pretext for the manufacturers to withdraw these drugs from the market. Recent examples of such industry responses to low demand are the withdrawal of Novolin R penfills in the U.K. and of Novolin 70/30 in several European countries. Thus, to recapitulate, given its cost-effectiveness, we consider NPH insulin the preferred agent for the initiation of insulin therapy in type 2 diabetes. However, if dose titration is limited by (nocturnal) hypoglycemia, a switch to a long-acting insulin analog should be tried.

There is doubt as to whether a once-daily dose of insulin detemir will help as many people achieve good control as NPH insulin and glargine. In a "treat-to-target" trial with twice-daily detemir administration, an end point A1C of 6.8% was reached (28). In other studies, a second daily detemir injection was required in 34–55% of study subjects because of predinner hyperglycemia or nocturnal hypoglycemia (29,32). In the only reported trial that investigated the efficacy of once-daily insulin detemir, A1C remained above the currently recommended glycemic goal with an end point level of 7.4%, both for NPH insulin and detemir (33), compared with an end of study A1C <7.0% with once-daily glargine and NPH in the original Treat-to-Target Trial (27). Rather than possible insufficiency of a once-daily dose of insulin detemir, these discrepant outcomes are likely to be explained by diversity in study design, such as different titration targets and titration frequency. This is supported by Figs. 1*A* and *B*, which show the relationship between the reduction in A1C level and end point insulin dose, and between A1C reduction and the frequency of patient contact, respectively, in nine randomized trials investigating insulin initiation with basal insulin (27–29,32–37). Both graphs show clear dose-response relationships, suggesting that substantial decreases in A1C can be achieved, provided that the daily insulin dose and the contact frequency are adequate. The only way to finally determine whether once-daily detemir injection is appropriate for the treatment of type 2 diabetes is to conduct a clinical trial, ideally comparing once-daily detemir and
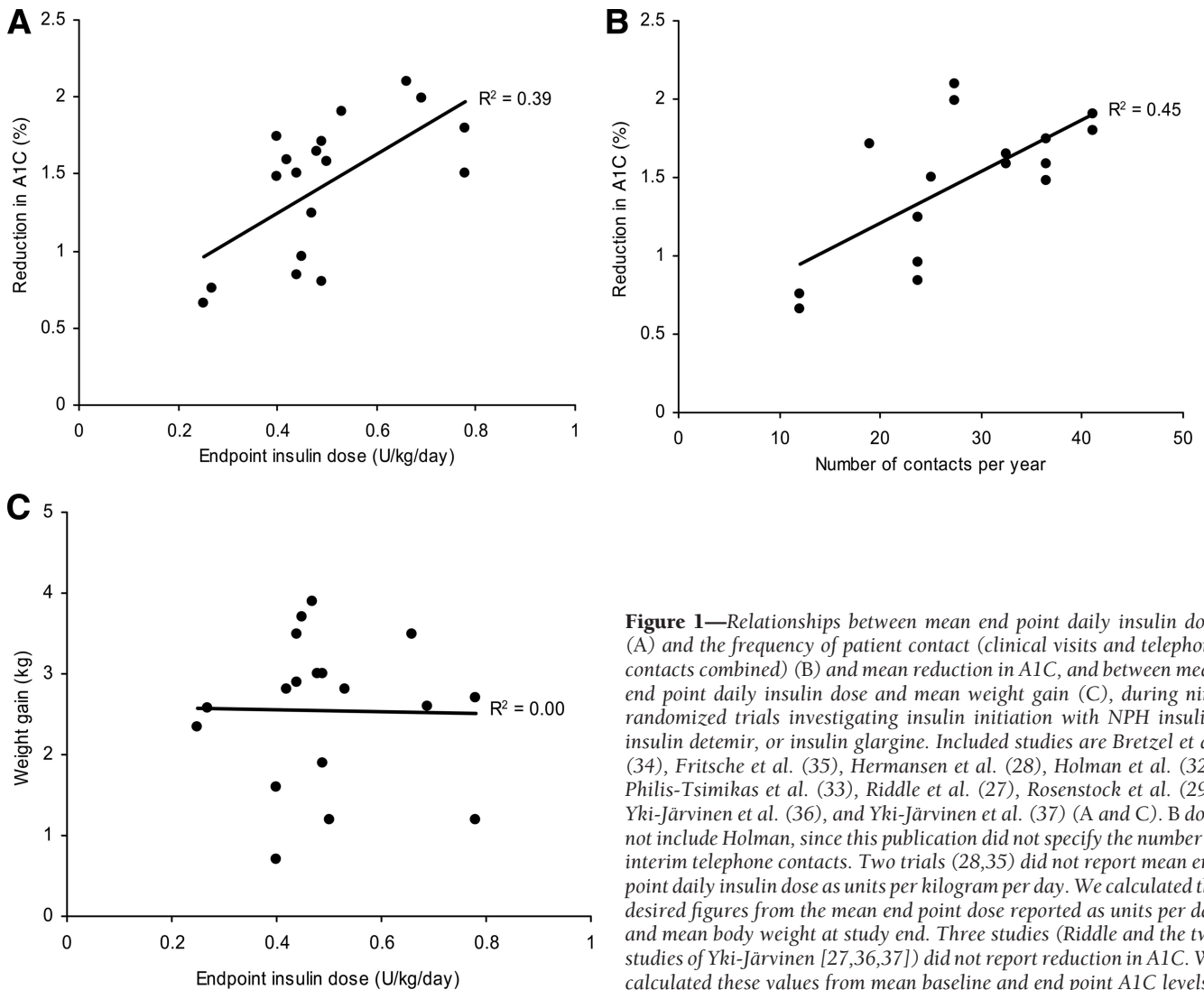
Figure 1—*Relationships between mean end point daily insulin dose (A) and the frequency of patient contact (clinical visits and telephone contacts combined) (B) and mean reduction in A1C, and between mean end point daily insulin dose and mean weight gain (C), during nine randomized trials investigating insulin initiation with NPH insulin, insulin detemir, or insulin glargine. Included studies are Bretzel et al. (34), Fritsche et al. (35), Hermansen et al. (28), Holman et al. (32), Philis-Tsimikas et al. (33), Riddle et al. (27), Rosenstock et al. (29), Yki-Järvinen et al. (36), and Yki-Järvinen et al. (37) (A and C). B does not include Holman, since this publication did not specify the number of interim telephone contacts. Two trials (28,35) did not report mean end point daily insulin dose as units per kilogram per day. We calculated the desired figures from the mean end point dose reported as units per day and mean body weight at study end. Three studies (Riddle and the two studies of Yki-Järvinen [27,36,37]) did not report reduction in A1C. We calculated these values from mean baseline and end point A1C levels.*

glargine in patients with baseline A1C levels of ~8.5%. Such a study could also assess whether higher detemir dosages are needed to obtain the same level of glycemic control as with insulin glargine, as was demonstrated in two of the aforementioned studies in which detemir was administered twice daily (28,29,38). This trial could also confirm the proclaimed reduction in weight gain associated with insulin detemir.

Titration and timing of basal insulin
After the recent unexpected finding of increased mortality in the intensive glucose-lowering therapy group of the ACCORD study, which might be partly related to the rate of the reduction in A1C (6), clinicians may now be more reserved to lower glucose levels promptly. However, we still feel that in addition to timely initiation, rapid titration of the dose is indispensable for successful insulin therapy. The ACCORD study

solely included patients at high risk for cardiovascular disease, in whom low A1C levels were reached by using up to four or five different classes of glucose-lowering drugs. In contrast, in less selected patients treated with stable doses of one or two oral agents, simple titration algorithms targeting fasting plasma glucose ≤100 mg/dl (≤5.6 mmol/l) can safely achieve A1C of 7.0% (27). A patient-driven algorithm, with patients increasing their insulin dose by 2 or 3 units every 3 days, as long as their fasting plasma glucose remains above target, constitutes a practical approach that has been shown to be equally or more effective than physician-led titration (39,40).

Regarding the timing of injection in once-daily basal insulin regimens, administration of NPH in the evening appears to be superior to morning injection (11,25). Studies examining the injection time of the long-acting insulin analogs showed conflicting results. One study conducted with

insulin glargine found greater reductions in A1C and nocturnal hypoglycemia with morning compared with evening injection (35), whereas a larger comparison of morning versus evening glargine with an identical study design did not find any difference (both studies investigated this issue against a background of glimepiride once daily) (41). A morning administration of insulin detemir was associated with lower glucose levels during the day and a trend toward a reduced risk of nocturnal hypoglycemia compared with evening injection (33). From these discrepant data, it can be concluded that when nocturnal hypoglycemia limits dose titration of evening detemir or glargine, administration in the morning could be attempted.

Other options for the initiation of insulin therapy
The recent Treating to Target in type 2 Diabetes (4-T) study compared the intro-

duction of basal insulin at bedtime to insulin initiation with either biphasic insulin twice daily or prandial insulin before meals (32). The biphasic and prandial insulin regimens provided better glycemic control than once-daily basal insulin (escalated to twice daily in 34% of patients) but at the expense of increased risks of hypoglycemia and weight gain. Although biphasic insulin reduced A1C levels to the same extent as prandial insulin, the latter regimen was associated with the most hypoglycemic episodes and the highest weight gain (32). Therefore, and considering that to date there is no clinical trial evidence supporting the specific lowering of postprandial glucose levels when aiming to lower cardiovascular risk in type 2 diabetes, initiation with prandial insulin is generally not a first-choice approach when starting insulin in type 2 diabetic patients. This was confirmed by a recently reported direct comparison of once-daily insulin glargine versus thrice-daily insulin lispro in insulin-naive patients (34). Finally, also regarding feasibility in clinical practice and patients' acceptance, three injections per day is the least attractive option for initiation of insulin therapy.

Although many are accustomed to initiation with biphasic insulin, we generally recommend the addition of once-daily basal insulin to oral therapy for several reasons. First, the lower A1C levels reached with biphasic insulin comes at the expense of increased risks of hypoglycemia and weight gain (32,42,43). Second, and as aforementioned, trials with systematic dose titration demonstrated that once-daily basal insulin achieves the currently recommended glycemic levels in many patients with type 2 diabetes (27,29). In this respect, it has frequently been argued that in patients with badly controlled hyperglycemia (e.g., A1C >8.5% at the start of insulin therapy), treatment with once-daily basal insulin alone would not attain glycemic goals (11,32,33). However, the LANMET study proved otherwise. In this clinical trial, A1C levels decreased from 9.1% at baseline to 7.1% with combination therapy of bedtime insulin glargine or NPH insulin and metformin (36). Finally, it seems likely that insulin initiation by means of one (basal) injection may also facilitate patients' acceptance of insulin initiation.

Combined therapy with oral agents
As discussed at the first Controversies in Obesity, Diabetes and Hypertension

(CODHy) meeting, the rationale for combining insulin with oral therapy is minimization of the adverse effects of insulin treatment, i.e., hypoglycemia and weight gain (44). Combination of insulin with metformin is indeed associated with better glycemic control, fewer hypoglycemic events, and less weight gain than treatment with insulin alone (45). Therefore, metformin should be continued when patients are initiated on insulin therapy (i.e., providing there are no intolerable side effects). Data concerning the combination of insulin with either sulfonylureas alone, or with both metformin and sulfonylureas, compared with insulin-alone treatment regimens, are ambiguous (46). The only consistent advantage of such combined therapy is reduced insulin dose requirements, which may result in less daily injections, easier dose titration, and improved compliance (46). However, these potential benefits must be balanced against the side effects and higher cost of continuing sulfonylureas together with metformin compared with treatment with metformin and NPH insulin alone—although not versus long-acting insulin analogs and metformin alone (31,46)—and the possibility of reduced patient adherence when increasing numbers of pills are prescribed (47). An ongoing randomized trial comparing the continuation of sulfonylureas in combination with metformin and insulin glargine versus discontinuation of sulfonylureas with this combination regimen in insulin-naive type 2 diabetic patients will hopefully provide further evidence regarding this issue (ISRCTN29335793: www.controlledtrials.com).

INTENSIFICATION OF INSULIN THERAPY

When should insulin therapy be intensified?
Because of progressive β-cell decline, treatment with once-daily basal insulin alone will eventually fail to maintain glycemic control in a substantial number of patients with type 2 diabetes. When the recommended A1C level of <7.0% is not reached, or maintained despite successful basal insulin dose titration maintaining fasting plasma glucose ≤100 mg/dl, or when aggressive titration is limited by hypoglycemia, treatment should be intensified by adding insulin injections.

How should insulin therapy be intensified?
The available options for additional insulin injections include a second injection of basal insulin, prandial insulin before one or more meals, or a switch to biphasic insulin. The choice between intensification of basal insulin versus the introduction of prandial or biphasic insulin should be individualized based on patients' diurnal blood glucose profiles. When considering the profiles obtained with NPH insulin or long-acting insulin analog once daily, the effect appears to wane during the day, even in patients starting insulin therapy, i.e., with remaining endogenous insulin secretion (33,37,48). These patients could benefit from adding a second injection of basal insulin (48). However, in the context of declining endogenous insulin secretion, daytime hyperglycemia is usually related to elevated postprandial glucose levels, favoring the initiation of prandial or biphasic insulin.

Two recent studies established that in patients not achieving adequate glycemic control with once-daily basal insulin, basal-bolus therapy results in greater A1C reductions than biphasic insulin twice or thrice daily (49,50). However, when a more gradual intensification of insulin treatment is preferred, patients can be switched to biphasic insulin two, and subsequently three, times daily. The latter regimen has been shown to significantly improve A1C levels of patients previously treated with insulin glargine (50). Whether stepwise introduction of mealtime injections is as safe and effective as the rapid initiation of a full basal-bolus regimen is currently under investigation (51).

Finally, regarding the choice of prandial insulin, rapid-acting insulin analogs are not superior to regular insulin in reducing A1C levels or rates for overall and nocturnal hypoglycemia, despite improving postprandial control (18). In some studies, treatment with rapid-acting analogs was associated with fewer severe hypoglycemic episodes and improved treatment satisfaction (18), the latter probably being related to increased convenience because of injection immediately before meals. In conclusion, there is no compelling reason to overall favor rapid-acting insulin analogs over regular insulin in type 2 diabetes. Whereas in some countries the price of rapid-acting analogs has been lowered to the level of regular insulin, in others, it remains around twice as high (31).

Continuous subcutaneous insulin infusion

In patients with type 2 diabetes already using at least one daily insulin injection, the introduction of intensive insulin therapy with continuous subcutaneous insulin infusion resulted in comparable glycemic control, weight gain, and hypoglycemia risk as multiple daily injection therapy (52,53). Although continuous subcutaneous insulin infusion was associated with greater improvements in treatment satisfaction in one study (53), we recommend that its use be restricted to selected patients in experienced centers only.

DRAWBACKS OF INSULIN THERAPY

Hypoglycemia

Intensive glucose-lowering therapy inevitably results in an increased rate of hypoglycemia, which was once again confirmed in the recent ACCORD study with annualized rates of hypoglycemic episodes requiring medical assistance of 3.1 and 1.0% in the intensive and standard therapy groups, respectively (6). Iatrogenic hypoglycemia hampers tight glycemic control and is considered the limiting factor in diabetes management (54).

Opinions are divided on the extent of the problem, with cited event rates for severe hypoglycemia in insulin-treated type 2 diabetic patients ranging from between 1 and 3 (5) to between 10 and 73 per 100 patient-years (55). Of note, the relatively low rates were found in clinical trials (2,56), whereas the higher figures were reported in retrospective and population-based studies (57–59). The difference is probably explained by varying durations of disease or insulin therapy in the cited studies. The risks of mild and severe hypoglycemia are low among type 2 diabetic patients just beginning insulin therapy (30) and appear to increase with increasing durations of diabetes and insulin treatment (57–59).

To conclude, in type 2 diabetes, the frequency of hypoglycemia is generally lower than that in type 1 diabetes (54). This is presumably the result of relative protection of type 2 diabetic patients against hypoglycemia by residual endogenous (i.e., physiologically regulated) insulin and glucagon secretion, insulin resistance, and higher glycemic thresholds for counterregulatory and symptomatic responses to hypoglycemia (60,61). Therefore, when initiating insulin therapy, attempts to attain A1C goals should not be hampered too much by concerns about hypoglycemia. However, iatrogenic hypoglycemia appears to become a more frequent problem at the insulin-deficient stage of the disease, warranting more vigilance as the disease advances (54).

Weight gain

The ~2- to 4-kg increase in body weight associated with insulin therapy has traditionally been explained by reductions of glucosuria and resting energy expenditure when glycemic control is improved (5,46). Other explanations are snacking to prevent, or in response to, hypoglycemia or restoration of the weight loss usually preceding insulin initiation to the weight before onset of diabetes. In contrast, a recent study found that the mean weight gain of 1.8 kg in 23 type 2 diabetic patients during the first 6 months of insulin therapy was not accompanied by a change in glucosuria, resting energy expenditure, or physical activity. The authors concluded that increased energy intake was the only plausible explanation for the observed weight increments (62). Although the mechanisms underlying insulin-associated weight gain are still not fully understood, it is thought to be proportional to the number of insulin injections, or the total daily insulin dose (32,45,46). Interestingly, when considering studies investigating basal insulin initiation in type 2 diabetes, we found no evidence for such a dose-response relationship (Fig. 1*C*).

Finally, when directly comparing the mean increases in body weight during insulin initiation with NPH insulin versus long-acting insulin analogs, insulin glargine is associated with similar weight gain (27,35–37). Treatment with insulin detemir, on the other hand, appears to result in less weight gain than NPH insulin (28,33). However, considering the limited magnitude of the reported weight-sparing effect, we still recommend NPH insulin for the initiation of insulin therapy in patients with type 2 diabetes.

CONCLUSIONS — Although insulin has no upper dose limit and numerous trials established that glycemic goals can be attained by using adequate doses, in clinical practice, many patients experience years of uncontrolled hyperglycemia.

Because most type 2 diabetic patients have residual endogenous insulin secretion, the rationale for imitating the physiological insulin secretion pattern is less convincing than in type 1 diabetes.

Glycemic treatment should be stepwise with swift introduction of successive interventions after treatment failure (i.e., A1C ≥7.0%). Insulin should be initiated when A1C is ≥7.0% after 2–3 months of dual oral therapy. The preferred regimen for insulin initiation in type 2 diabetes is once-daily basal insulin. In addition to timely initiation, rapid titration of the dose is indispensable for successful insulin therapy. Hypoglycemia risk is very low among type 2 diabetic patients just starting insulin therapy, making NPH insulin the most cost-effective drug.

When glycemic goals are not attained despite successful basal insulin dose titration (i.e., fasting plasma glucose ≤100 mg/dl), or when titration is limited by hypoglycemia, treatment should be intensified by addition of prandial or biphasic insulin.

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