Pivotal Role of Timely Basal Insulin Replacement After Metformin Failure in Sustaining Long-Term Blood Glucose Control at a Target in Type 2 Diabetes

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Type 2 diabetes over time associates with the development of vascular complications (1). The causative role of long-term elevation of blood glucose is well established, at least for microvascular complications, since intervention strategies directed at reducing hyperglycemia lower onset and/or progression of microangiopathy (1,2). The role of hyperglycemia and its treatment in the development of macrovascular complications is less well established. In fact, it takes a longer time to observe a positive effect of better blood glucose control (in addition to reducing the multiple risk factors often associated with type 2 diabetes such as hypertension, visceral obesity, and hyperdyslipidemia) on macroangiopathy compared with microangiopathy (1,3,4). Today's understanding of the complex relationship between hyperglycemia and complications in type 2 diabetes predicates that only an early and aggressive blood glucose–lowering intervention (in addition to reduction of the above mentioned risk factors), successfully sustained over time, will translate into benefits on macrovascular complications several years later (likely 10–15 years) (1,3–5). Thus, the present recommendation is to intensively treat people with type 2 diabetes from the clinical onset of the disease, particularly subjects with short diabetes duration who likely have not yet developed vascular complications and who presumably have a long life-expectancy (6).

At present, the question is not *whether* to intensively treat people with type 2 diabetes at onset of the disease to prevent long-term complications. The question rather is *how* to intensively treat type 2 diabetes over the many years and decades of the progression of the disease to consistently keep A1C levels <7.0% over the entire cycle of type 2 diabetes. At present, this question is difficult to answer, primarily because of the lack of evidence of long-term effects of one specific intervention, compared with several other possible intervention strategies (7) in type 2 diabetes. In addition, one should always keep in mind that type 2 diabetes is a complex disease characterized by large heterogeneity among individuals and variable progression over time that may eventually result in a nearly total loss of pancreatic β-cell function in just a few years (8,9).

THE AMERICAN DIABETES ASSOCIATION–EUROPEAN ASSOCIATION FOR THE STUDY OF DIABETES CONSENSUS

—The 2008 consensus of the American Diabetes Association (ADA)–European Association for the Study of Diabetes (EASD) (7) proposes lifestyle intervention along with metformin at diagnosis of type 2 diabetes to rapidly reduce A1C levels to <7.0%. This "step 1" is generally well accepted, and, in fact, it is common clinical experience that combining medical nutrition treatment and physical exercise, along with metformin, reduces A1C to <7.0% in a significant number of subjects. However, in subjects presenting with severely elevated blood glucose (A1C >9–10%), initiation of insulin controls hyperglycemia more rapidly than oral hypoglycemic agents (10).

Some patients never satisfactorily respond to lifestyle modifications and metformin and do not reduce A1C to <7.0% within a few months of treatment initiation. Other patients, after an initial successful response to lifestyle modification + metformin, may lose the response within months or a few years; therefore, their A1C progressively increases beyond the value of 7.0%. This is the time at which an aggressive "add on" treatment has to be initiated to rapidly control A1C to <7.0% and maintain it over a long period of time ("step 2" of the ADA-EASD consensus) (6). To successfully implement step 2, several preliminary considerations should be made. First, the initiation of step 2 should be timely, i.e., the decision should be made as early as possible after failure of step 1 to maintain A1C <7.0%. This scenario requires consistent monitoring of A1C every 2–3 months, which makes it possible to identify the trend for progressive increases of A1C from values of 6–6.5 to 7.0%. Perhaps it would be better to move to step 2 immediately before, not after, A1C has already trespassed the threshold of 7.0%.

OPTIONS IN STEP 2 OF THE ADA-EASD CONSENSUS

—In step 2, the simplest option is addition of a second oral agent, either a sulfonylurea (SU) or a thiazolidinedione (7). This addition will likely reduce A1C to <7.0% in some patients, but the durability is questionable. Although combinations of two

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drugs have not been examined, the durability of single oral agents is quite limited over time (11). Perhaps the most rational combination would be adding a dipeptidyl peptidase (DPP)-4 inhibitor, not an SU, on top of metformin. This step would reduce the SU-related hypoglycemia risk for similar glycemic control (12) and also the risk for apoptosis of pancreatic β-cells with SU demonstrated at least in vitro (13) and invoked to explain the short durability of SU in vivo (11). Based on this kind of observation, one might anticipate that in type 2 diabetes, β-cell function would benefit long term simply by not using an SU and considering alternative options that resulted in similar glycemic control. However, the interesting hypothesis of superiority of DPP-4 inhibitors over SU in terms of durability of β-cell function over time in type 2 diabetes is still to be demonstrated. At present, use of DPP-4 inhibitors is limited because of cost.

The second option in step 2 is injectable, i.e., either insulin (as basal preparation) or a glucagon-like peptide (GLP)-1 agonist (7). Several studies have compared head-to-head treatments with basal insulin versus GLP-1 agonists in type 2 diabetes (14–17). However, at present, there are not clear recommendations when it would be more convenient to initiate patients with basal insulin compared with GLP-1 agonists.

OUTCOMES OF CLINICAL STUDIES COMPARING BASAL INSULIN AND GLP-1 AGONISTS IN TYPE 2 DIABETES

—The demonstration of the elegant physiology of the incretin system in the regulation of blood glucose homeostasis (18) has prompted research to develop GLP-1 agonists for treatment of type 2 diabetes, with successful improvement of blood glucose primarily in the postprandial situation, but to some extent also in the fasting state (14–17).

Although GLP-1 agonists and basal insulin treatments both reduce A1C by a similar extent (14–17), there are relevant differences in terms of other outcomes. Individual GLP-1 agonists have different effects, but as a class, all GLP-1 analogs result in loss of body weight, in contrast to the increase in body weight with basal insulin; they all reduce the risk of hypoglycemia compared with basal insulin; and they do not require dose titration, and therefore blood glucose monitoring is theoretically not necessary, at least when given in monotherapy, in contrast to basal insulin. However, these benefits of GLP-1 analogs have to be weighed against their relevant side effects, primarily the limited tolerability in a significant number of patients (gastrointestinal side effects). In addition, the elevated cost restricts the treatment to a minority of wealthy type 2 diabetic patients (and/or countries). Finally, experience with GLP-1 agonists is limited, and durability of such a treatment is unknown. In contrast, (basal) insulin has no limitations in terms of tolerability (except for hypoglycemia) and durability (except possibly requiring the addition of prandial insulin) and is a rather cheap treatment.

BENEFITS OF INITIATION WITH INSULIN (BASAL) OF STEP 2 OF THE ADA-EASD CONSENSUS

—Insulin (basal) can easily be initiated immediately after failure of metformin (and lifestyle intervention), thus bypassing the add-on treatment of SU, although it is reasonable to consider the more traditional use of insulin after failure of the combination metformin + SU (or DPP-4 inhibitor). In fact, although SUs are effective, very popular, and cheap, and there have been decades of experience with their use, they have negative aspects. SUs stimulate insulin secretion in a rather glucose-independent manner, in contrast to incretins (19); thus, they do not specifically target postprandial hyperglycemia, but rather fasting blood glucose. Most importantly, they increase hypoglycemic risk (7,19), and last, but not least, there is evidence at least in vitro that they increase apoptosis (13).

Insulin (basal) has a number of benefits when initiated at step 2 of type 2 diabetes treatment. Insulin (basal) easily lowers in a predictable dose-dependent manner both fasting blood glucose and to some extent postprandial blood glucose, thus reducing the 24-h mean blood glucose concentration and A1C (20). The administration of insulin is painless and the titration of the basal preparation is simple, with low risk for hypoglycemia. Insulin dose can be tailored to individual needs on a unit-to-unit basis (21). In contrast to other drugs, there is no intolerance or adverse effects to insulin. Insulin has been in use for nearly 90 years, which is the longest experience than with any other drug, with the notable exceptions of digitalis and aspirin.

Insulin has relevant extra-glucose beneficial effects that make insulin unique, although GLP-1 agonists may have some effects beyond glucose (Table 1). Insulin is the only drug that directly reduces lipolysis and free fatty acid concentrations in blood (22), thus reducing lipotoxicity (23) and improving insulin action and secretion (24) and the liver fat accumulation in non-alcoholic steato-hepatitis (25). In addition, it improves lipoprotein metabolism (26), decreases LDL cholesterol and triglycerides, and increases HDL cholesterol (27). Insulin promotes nitric oxide synthesis by endothelium, thus reversing endothelial dysfunction of type 2 diabetes (28), a well-known cardiovascular risk factor (29). No other hypoglycemic drug has such a large number of pleiotropic effects in the treatment of type 2 diabetes.

Insulin, including basal insulin, also has drawbacks—namely the risk for hypoglycemia and weight gain. However, the hypoglycemia risk is associated primarily with prandial and premixed, not basal, insulin treatment (30,31). Although the risk for hypoglycemia is higher with basal insulin than with GLP-1 analogs (14,15), the absolute events are

Table 1—*Comparison of positive and negative effects of basal insulin compared with GLP-1 treatment in type 2 diabetes*

	Positive	Negative
Insulin	Lowers blood glucose	Increases body weight and risk for hypoglycemia
	Lowers free fatty acids	
	Increases HDL/decreases LDL cholesterol	
	Decreases hepatic fat content in NASH	
	Increases hepatic and muscle insulin sensitivity	
	Improves pancreatic islet β-cell function	
	Reverses endothelial dysfunction	
GLP-1 agonists	Lower blood glucose similarly to basal insulin	Limited tolerability
	Reduce body weight	Expensive
	Virtually no hypoglycemia	Short-term experience

NASH, non-alcoholic steato-hepatitis.

infrequent, especially with long-acting insulin analogs compared with NPH (32). Weight gain increases between 2 and 4 kg on insulin treatment (30,31,33), whereas with GLP-1 agonists, there is a decrease of similar magnitude (14–17). However, the weight gain on insulin is associated with improved insulin sensitivity, better plasma lipids, and improved glycemic control, as mentioned above. Altogether, these observations account for the overall decrease in cardiovascular risk on long-term insulin treatment despite some weight gain in interventional studies (1,6).

SUPERIORITY OF BASAL INSULIN COMPARED WITH PRANDIAL AND PREMIXED INSULIN

—Although similar A1C values can be achieved after initiation of basal or prandial insulin, basal is more convenient than prandial (30,31) and premixed (31,34) insulin because of the lower increased body weight, the lower hypoglycemia risk, and the lower need for blood glucose monitoring. Those patients who are not at target, or who can no longer control A1C on basal insulin only, should add prandial insulin to basal (35), not switch to premixes (36). In fact, although aggressive titration of premixed insulin can lower A1C to target (33) or near-to-target (31), this result is associated with elevated frequency of hypoglycemia (31,34) due to inappropriate pharmacokinetics and pharmacodynamics, primarily in the interprandial state of the late-morning and early-night hours (37).

DIFFERENCES BETWEEN BASAL INSULINS

—The old NPH and the new long-acting insulin analogs glargine and detemir similarly decrease A1C to target in type 2 diabetes (32). However, both analogs are superior to NPH, because for the same A1C achieved, they reduce the risk of hypoglycemia compared with NPH (32). On the other hand, the curvilinear relationship between A1C and frequency for hypoglycemia with basal insulins (38,39) also indicates that for the same frequency of hypoglycemia, A1C is consistently lower with both analogs—glargine and detemir versus NPH. All of these observations indicate that any level of A1C achieved with a given insulin preparation or treatment should be analyzed not in absolute, but rather in relative terms, taking into account the frequency of hypoglycemia observed for each level of A1C achieved.

Recently, the pharmacokinetics and pharmacodynamics of therapeutic doses of the basal insulins NPH, glargine, and detemir have been examined in the only study comparing head-to-head basal insulins in type 2 diabetes (40). The pharmacodynamic effect of glargine on glucose metabolism is superior to that of detemir and NPH. Likewise, glargine better than detemir and NPH suppresses lipolysis and pancreatic α- and β-cell islet function. This latter effect of basal insulin likely is the mechanism of the protective effect of insulin on β-cell function in type 2 diabetes (10). Although all basal insulins have a similarly long median duration of action (>31 h), the intersubject variability of glargine is lower than that of detemir and NPH. Interestingly, none of the basal insulins stimulate glucose utilization, their pharmacodynamic effect being explained solely by suppression of hepatic glucose production. Finally, the nocturnal activity of NPH insulin indicates a peak of between 0100 and 0400 h, whereas glargine is peakless and detemir increases its activity overnight slowly after an initial lag phase (40), thus explaining the protection against risk of nocturnal hypoglycemia of the two analogs compared with NPH in clinical studies (32). Thus, the three basal insulins exhibit relevant differences not only in type 1 diabetes (32), but in type 2 diabetes as well (40). A recent study (41) has compared head-to-head NPH, glargine, and detemir with results at variance compared with those described above (40). However, this study (41) has investigated normal nondiabetic subjects who do not need basal insulin treatment in their daily life, and therefore the results remain applicable to normal subjects only and the data cannot be extrapolated to the wide spectrum of insulin deficiency and insulin resistance that characterizes subjects with type 1 diabetes (32) or type 2 diabetes (40).

CONCLUSIONS

—After lifestyle modification and metformin fail to sustain A1C to <7.0%, insulin (basal) should be initiated in a timely manner and preferred to the other options in step 2. Metformin should be continued (whenever tolerated and/or not contraindicated) when insulin is initiated, because of the well-demonstrated multiple benefits on reduction of body weight and A1C and lower risk for macrovascular events (42).

The recommendation of early use of insulin in type 2 diabetes emphasized in this article still requires large prospective trials in Caucasians to confirm the benefits observed in the Chinese population (10). Nevertheless, today is not too early for an "early initiation" of insulin in type 2 diabetes. The traditional view of insulin as a late or "last resort" in type 2 diabetes should be opposed in the year 2011, i.e., in an era where we have learned about the possibility of prevention of complications by early institution of strict glycemic control and β-cell protection.

The alternative choice is treatment with GLP-1 agonists. This choice is appealing because of its efficacy, possible weight loss, and low risk for hypoglycemia. However, the limitations of GLP-1 agonists (Table 1) make this a second choice of step 2 compared with basal insulin, with the notable exception of obese subjects with type 2 diabetes.

The present dualism, i.e., choice between basal insulin versus GLP-1 agonists, will likely be replaced in the near future by combination strategies where GLP-1 agonists would be added to basal insulin. In physiology, incretins cooperate with insulin in glucose homeostasis in the fasting and, to a larger extent, postprandial situation (18). In fact, in type 2 diabetes, addition of a DPP-4 inhibitor or GLP-1 agonists improves short-term postprandial blood glucose (43). Addition of GLP-1 agonists to basal insulin improves long-term A1C in subjects who cannot reach the target despite optimization of basal insulin (44). Although additional studies are needed to learn more about this potentially rational and synergistic combination in subjects with type 2 diabetes with different characteristics and of long duration, it is likely that in the near future, GLP-1 agonists will be combined early with basal insulin in step 2 of the consensus (7). The goals are reducing or even neutralizing the increase in body weight observed with basal insulin and lowering more blood glucose, especially in the postprandial state, thus reducing A1C further compared with basal insulin only. Notably, these additive effects of GLP-1 occur in the absence of the greater hypoglycemia risk (45) observed when SU or prandial insulin are added to basal insulin (20,30,31). If this were the case, then incretins, namely GLP-1 agonists, would become the add-on treatment of choice when basal insulin alone is no longer able to reduce A1C to <7.0%. Addition of GLP-1 under these circumstances

would prevent use of SU or rapid-acting insulin at mealtime. The main benefit of such a combination would be reducing hypoglycemic risk whenever targeting an A1C level of <7.0%. At present, such a risk increases considerably because intensification of treatment is based on SU and/or basal-bolus or premixed insulin regimens (45). Thus, a future treatment paradigm of type 2 diabetes after basal insulin might foresee no add-on of SU and use of prandial insulin on top of basal at a later stage when the response to GLP-1 is lost.

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