Insulin Therapy in People With Type 2 Diabetes: Opportunities and Challenges?

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Given the continued interest in defining the optimal management of individuals with type 2 diabetes, the Editor of *Diabetes Care* convened a working party of diabetes specialists to examine this topic in the context of insulin therapy. This was prompted by recent new evidence on the use of insulin in such people. The group was aware of evidence that the benefits of insulin therapy are still usually offered late, and thus the aim of the discussion was how to define the optimal timing and basis for decisions regarding insulin and to apply these concepts in practice. It was noted that recent evidence had built upon that of the previous decades, together confirming the benefits and safety of insulin therapy, albeit with concerns about the potential for hypoglycemia and gain in body weight. Insulin offers a unique ability to control hyperglycemia, being used from the time of diagnosis in some circumstances, when metabolic control is disturbed by medical illness, procedures, or therapy, as well as in the longer term in ambulatory care. For those previously starting insulin, various other forms of therapy can be added later, which offer complementary effects appropriate to individual needs. Here we review current evidence and circumstances in which insulin can be used, consider individualized choices of alternatives and combination regimens, and offer some guidance on personalized targets and tactics for glycemic control in type 2 diabetes.

The ultimate goal of diabetes management is prevention of long-term complications. An important means to this end is improvement and maintenance of glycemic control over time. Unfortunately, this is not a simple task due to the progressive nature of the disease, which requires timely optimization of treatment, leading in a majority of cases to insulin therapy. Various forces oppose and thus delay starting insulin, and the lag between the time insulin is needed and the time it is used has been described as due to "clinical inertia" (1). Shah et al. (2) have reported that less than one-half of patients with high HbA_{1c} levels have their treatment optimized even when specialists manage their condition. However, in that study, specialists were more active in prescribing insulin than primary care physicians. Nonetheless, in all areas of clinical practice, use of insulin tends to be delayed and irreversible complications can already be present by the time it is started. In a multinational survey involving >66,000 diabetic patients, average HbA_{1c} at the time of beginning insulin was 80 mmol/mol (9.5%) and ~90% of the participants already had some kind of complication (3). Various concerns serve as barriers to starting insulin, and often it is a physician rather than the patient who decides to postpone insulin therapy (4).

The specific point at which insulin therapy should begin can be difficult to define for an individual person, and universal guidance has proved elusive. Type 2 diabetes is

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characterized by progressive β-cell (β-cell) failure, but the natural history of β-cell decline is variable and assessment of β-cell function is difficult. Beyond the problem of assessing the need for insulin, exogenous insulin has potential effects that frequently worry both people with diabetes and health care professionals (4). These include hypoglycemia and weight gain. Fear of injections themselves and various negative connotations of insulin therapy, such as advanced disease and personal failure, also pose significant hurdles for some people despite modern injection devices. However, suggestion of a need to increase self-monitoring, and thus finger pricking, to support optimization of insulin have ameliorated injection problems to some degree. Finally, educational support for starting injections and adjusting the dosage of insulin is not easily available to all people.

GROWING EVIDENCE FOR INSULIN THERAPY

As noted above, a commonly accepted view is that type 2 diabetes develops when insulin secretion can no longer compensate for the underlying metabolic disturbance. As secretory capacity progressively declines with time (5), it is understood that most people with type 2 diabetes will eventually require insulin therapy. Increasing use of therapies to protect against cardiovascular disease is extending the life of people with diabetes (6), and consequently more people will come to need insulin therapy. Diagnosis at a younger age will also extend the time of active treatment of diabetes. The effect of use of insulin in type 2 diabetes from the time of diagnosis has been evaluated in clinical trials, notably the UK Prospective Diabetes Study (UKPDS) and Outcome Reduction With Initial Glargine Intervention (ORIGIN) (7–9). UKPDS showed that early and continued glucose control can reduce microvascular complications and, in the long-term, improve cardiovascular prognosis (7,10). The beneficial effect of insulin therapy is further supported by studies in type 1 diabetes where it is apparent that if insulin therapy is used effectively to induce early glycemic control, both micro- and macrovascular protection is achieved (11). Although it is acknowledged that achieving HbA_{1c} $<$53 mmol/mol (7.0%) is a difficult task, improvement of glycemic control with insulin is associated with improved patient well-being even if the HbA_{1c} target is not achieved (12) (Table 1).

Short-term studies comparing insulins show that a high percentage of people with established type 2 diabetes not well controlled with oral therapies can achieve blood glucose control to target, and without high rates of hypoglycemia (13–15). Further, with optimization of dosage and timing, such control can be maintained for least 3 years, with hypoglycemia rates constant at ~10% of people with an event in a year (16). Observational studies show that in routine practice, HbA_{1c} of ~57 mmol/mol (7.4%) is achieved with little hypoglycemia in diverse countries around the world (3,17). Most recently, the ORIGIN trial introduced insulin therapy in people with relatively short-duration type 2 diabetes and high cardiovascular risk (9). With continuation of prior oral therapy and systematic titration of basal insulin (glargine), fasting glucose was kept at normal levels ($<$5.3 mmol/L) and median HbA_{1c} $\leq$45 mmol/mol (6.3%) for $>$6 years. Systematically intensified oral therapy, the comparator regimen in ORIGIN, also maintained very good control during this time. This study showed that despite maintaining very good glycemic control, insulin use was associated with a weight gain of a modest 2.1 kg more than on the oral regimen, the rate of hypoglycemia requiring assistance was modest (1% per year; $<$10% per year for nonsevere confirmed hypoglycemia), and there was no evidence of increased risk of malignancy or other serious adverse events. Adding the experience from ORIGIN to previous observations, particularly UKPDS, it can be argued that the evidence base for insulin is better than that for any other glucose-lowering agents, except perhaps metformin.

Even so, it must be acknowledged that although the safety and benefit of moderate doses of insulin in the long-term are clear (7,9,10), the use of high-dose insulin therapy, especially with mealtime injections, for people with obesity and severe insulin resistance might still be associated with adverse outcomes. Also, the evidence base does not satisfactorily address the answers to common questions that physicians ask themselves, such as whether it is time to start insulin or, alternatively, whether other therapies should be considered.

Another issue is what insulin and what insulin regimen should be chosen, perhaps bearing in mind the future need

Table 1—Summary of the evidence base for starting insulin in type 2 diabetes

Evidence type	Evidence findings
Strong observational and randomized clinical trial evidence	
	Insulin secretory capacity deteriorates with time (5)
	Insulin improves glycemic control in trials and in routine clinical practice (3,9,13,14,16)
	Improved glucose control improves HRQoL (12)
	LADA phenotype is associated with early need for insulin therapy (28)
Randomized clinical trial evidence of variable quality	
	Outcomes of acute illness are improved if glycemic control is better (61)
	Long-term medical outcomes are improved by better glycemic control (7,10,62)
	Glycemic control to $<$53 mmol/mol ($<$7.0%) HbA_{1c} is difficult to achieve and maintain with insulin (3,16)
	Insulin is successful in combination with oral agents and GLP-1RAs (49,63)
General knowledge and expert experience	
	Insulin treats and prevents ketoacidosis (64)
	Severe hyperglycemia predisposes to infection (53)
	Physician hesitancy in starting insulin therapy is a main barrier to insulin use (4)
	Patient preferences and views of injected therapies vary markedly (4)
	Insulin therapy can be tailored rapidly to changes in need during acute illness
	Insulin has potential powerful anabolic effects (wound healing, etc.)

HRQoL, health-related quality of life.

of optimization associated with the progression of the condition, and considering potentially high-risk subgroups for which specific tactics might be chosen. Basal insulins offer simplicity in injection frequency and ease of dose titration but may not be adequate to address postprandial excursions (15,18). This is particularly true with further loss of islet β-cell function, whence a mealtime + basal regimen will be needed, sometimes with mealtime insulin introduced meal by meal (16,19). Premixed insulins, started once or twice daily and occasionally increased to thrice daily, can offer a simpler approach where mealtime insulin is needed. However, premix insulins lack flexibility for dose adjustment and limit calibration of doses between the mealtime and basal needs. They also give a poorer basal insulin profile at night and more risk of daytime hypoglycemia compared with basal alone if mealtime insulin is not needed (20).

WHEN SHOULD INSULIN THERAPY BE STARTED?

Indications for insulin therapy and when to begin it are poorly defined in guidelines and still subject to individual judgment based on a wide range of opinion (21,22). Personal beliefs and experience, familiarity with the use of the different insulin preparations and delivery systems, individual preference, patient needle phobia, concern about chronic hyperinsulinemia, risk of hypoglycemia, and difficulties in controlling body weight are some of the many considerations regarding insulin therapy (4,23). Each one of these factors can be weighted differently between doctors and between people with diabetes. The expert group proposed that one way to rationalize the approach to insulin treatment could be to consider some clinical scenarios. These could be as follows: *1*) the time of diagnosis or early thereafter; *2*) in the presence of other emerging medical conditions; and *3*) in the course of routine ambulatory diabetes management.

Time of Diagnosis or Early Thereafter

In specific circumstances, insulin may be considered a potential first line therapy (Table 2 and Fig. 1) (24). Presentation of diabetes with ketonuria, with or without marked symptoms, should raise the suspicion of type 1 diabetes, although the possibility of accelerated lipolysis and ketogenesis due to starvation also deserves consideration. Ketoacidosis can be present at the time of diagnosis of type 2 diabetes, especially in the presence of another metabolic stress (i.e., myocardial infarction or infection or use of antiretroviral therapy). In such situations, immediate use of insulin is recommended and sometimes mandatory.

However, more common is the presentation of marked hyperglycemia with or without notable symptoms or ketonuria or advanced comorbidities (Fig. 1). Some guidelines suggest insulin is indicated for HbA_{1c} >69 mmol/mol (>8.5%) at diagnosis (24). This approach is not well substantiated by evidence, but it clearly can help by reducing glucose toxicity. Some evidence suggests short-term insulin therapy might help preserve β-cell mass, but this is probably still too speculative to influence clinical practice decisions (25). More substantial is evidence that restoration of nearly normal glucose levels with short-term administration of insulin at the time of diagnosis can allow recovery of β-cell function and improvement of insulin sensitivity sufficient to induce a clinical remission, during which lifestyle efforts either alone or with oral therapy can maintain control for some time (26,27).

Insulin is usually needed when diabetes is diagnosed in the context of an acute medical event causing acute metabolic deterioration, or in case of surgery or any other invasive procedure, temporarily or for longer term (Table 2 and Fig. 1). Some oral agents may be contraindicated in these situations, and insulin may be used to provide rapid and reliable control of the metabolic disturbance.

Lack of response or, even worse, further deterioration of glycemic control in spite of lifestyle modification and/or glucose-lowering agents should prompt consideration of the diagnosis of latent autoimmune diabetes in adults (LADA) (28). Measurement of glutamic acid decarboxylase (GAD) antibodies can confirm the diagnosis, but usually the clinical phenotype of low BMI, low waist circumference, little or no dyslipidemia (high triglycerides/low HDL cholesterol),

Table 2—"Algorithm" for starting/shifting insulin therapy

1. Is there an acute need?
   - Ketones (in absence of starvation)/ketoacidosis/dehydration
   - Marked hyperglycemia (without carbohydrate/calorie abuse)
   - Acute medical event with actual/potential decompensation
   - Marked hyperglycemia with uncertain near-future environment (foreign travel)

   →Strong immediate need—persuasive advice may be needed
2. Within ~2 years of diagnosis?
   - LADA phenotype or secondary pancreatic phenotype
   - Presence of GAD antibodies/low BMI/waist circumference/no dyslipidemia
   - Deterioration in glucose control in 6–24 months despite uptitration of multiple oral agent therapy
   - Concomitant disease: pancreatitis, hepatic cirrhosis, chronic steroid therapy, relapsing inflammatory disease, antirejection therapy, other

   →Discuss that insulin therapy will be inevitable or make medical self-management easier and safer—firm recommendation to start now
3. Taking one to four other glucose-lowering therapies and not to target (HbA_{1c} >58 mmol/mol [>7.5%])?
   - No other explanation for change in glucose control
   - Progression of hyperglycemia despite oral agent uptitration or neglected glucose control:
     - on three or more oral agents/GLP-1RA with HbA_{1c} above 58 mmol/mol (7.5%)
     - on two or more or more oral agents/GLP-1RA with deterioration of >8 mmol/mol (0.7%) HbA_{1c} since last seen without explanation
     - on one or more oral agent(s) with deterioration >11 mmol/mol (1.0%) HbA_{1c} since last seen without explanation
   - Previous patient education given and personal lifestyle input unlikely to improve
   - Patient preference for injectable natural hormone to drug

   →Discuss longer-term benefits of blood glucose control to target and efficacy (and tolerability issues) of insulin
     - o Consider alternative of a GLP-1RA (in particular if obese and happy to tolerate GI symptoms)
     - o With caution if hypoglycemia experienced on sulfonylureas

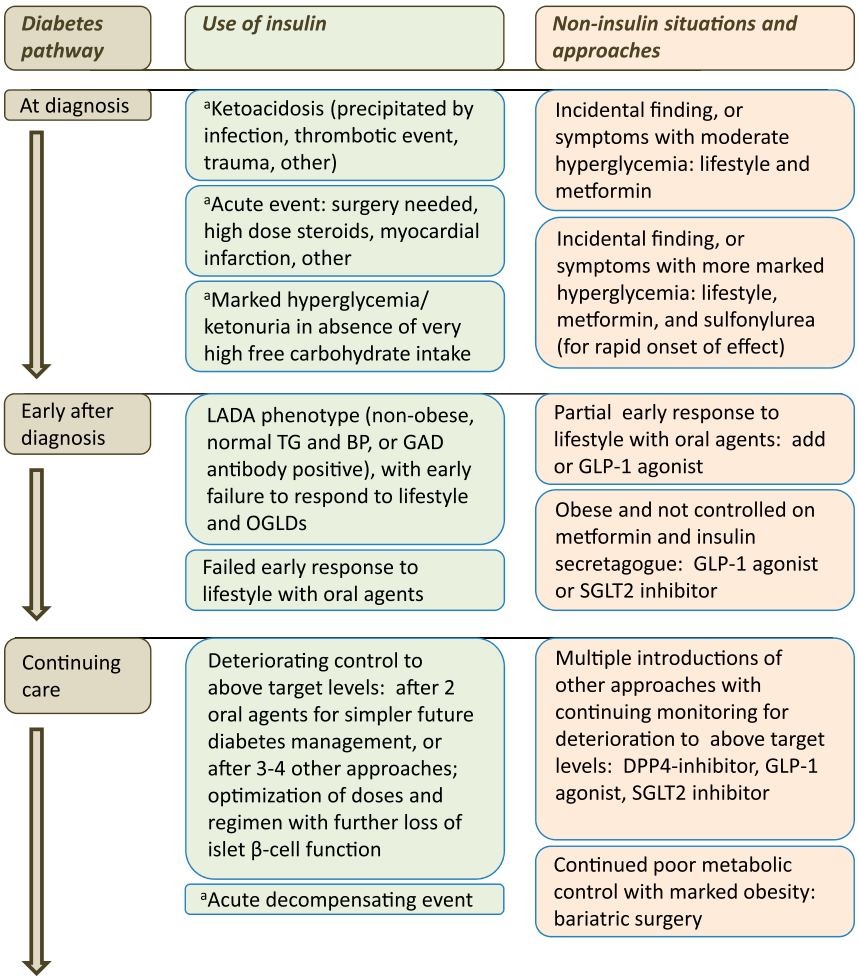

Figure 1—Summary of the use of insulin and other glucose-lowering approaches over the course of time in a person with type 2 diabetes. [a]use of insulin may be temporary. BP, blood pressure; OGLDs, oral glucose-lowering drugs; TG, triglyceride.

and lack of family history of diabetes is sufficient to raise suspicion. In these patients, insulin therapy can rapidly restore glycemic control and possibly slow the decline of insulin secretory function (28).

Presence of Other Nonacute Medical Conditions

People with a LADA-like phenotype (lean, relatively young, and no family history of diabetes) but without GAD antibodies could have secondary pancreatic diabetes due to acute or chronic pancreatitis or, more rarely, pancreatic cancer (Table 2). Other conditions potentially associated with the need for early insulin therapy include hepatic cirrhosis (29). In this setting, mealtime insulin is often needed to control postprandial hyperglycemia. People using glucocorticoid therapy, especially when taken intermittently at high dosage, quite often benefit from the power and flexibility of insulin therapy. Starting insulin can also ease blood glucose management during use of immune-suppressant therapy or antiretroviral therapies.

Ambulatory Diabetes Management

The more typical question is when to advise starting insulin for people taking two or three (or sometimes one or four) oral agents. Critical questions at this point are the level of glycemic control, rate of progression of hyperglycemia, available alternatives, and personal preferences (23). These will be modulated by concerns about and perhaps past experience with hypoglycemia (e.g., from prior use of a sulfonylurea), morbid obesity, concomitant disease, and life expectancy, all of which may influence the choice of therapy and personal glycemic targets (23).

Earlier and more rapid progression of hyperglycemia, perhaps evidenced by a more rapid need for multiple oral agents, suggests greater need for insulin (Table 2, item 3 and Fig. 1). For an individual who appears eligible for a "typical" glycemic target, such as HbA_{1c} <53 mmol/mol (<7.0%), it is reasonable to start thinking about insulin if HbA_{1c} is >58 mmol/mol (7.5%). If HbA_{1c} is >64 mmol/mol (8.0%), an additional oral agent will generally not be effective in reaching the target level unless lifestyle education has previously been neglected or adherence to lifestyle measures might improve, and thus insulin becomes a more attractive option. Because oral agents have limited efficacy, if glucose control is deteriorating rapidly, they may not be able to overtake the rate of deterioration, and in that case, insulin therapy may be preferable.

Individual preference may be to delay insulin by starting another treatment. When this is done, it is desirable to advise the patient that the plan will be reevaluated in 4–6 months. If glycemic control is then unacceptable, insulin should be recommended, usually with continuation of some of the other therapies.

The stepped algorithm for use of diabetes therapies with time does seem to get ever more complex, as the range of options increases with newer classes of glucose-lowering medications (24). One advantage of insulin therapy is often forgotten here, namely that since it is inevitable for the majority of individuals, starting it early, when people are only on one or two oral agents, considerably simplifies further management. Essentially recurrent decisions and assessments over which other class or individual medication to use are avoided for the most part, along with the problems of monitoring success and eventual "failure" of each of those other agents. Since however many medications are licensed in at least some major markets for combination with insulin therapy, starting insulin does not preclude the addition of dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1RAs), thiazolidinediones, or sodium/glucose cotransporter 2 (SGLT2) blockers, should a specific indication become clear while insulin is being used.

CONSIDERATION OF OTHER OPTIONS

The decision to start insulin therapy will not usually be taken in isolation. Indeed rather than "should insulin be started?", the most appropriate question is usually "which of a series of options is most appropriate for this person already on treatment but needing better blood glucose control?" In the above discussion, we consider situations in which insulin might be started, but in only a few (e.g., ketoacidosis or other acute metabolic disturbance or prospect thereof) will insulin be mandatory, although in many cases (pancreatic diabetes, suspected LADA, or intermittent steroid therapy), it can also be the simplest approach to manage in the medium-term (Fig. 1).

Further Lifestyle Advice and Oral Agents

At the time of diagnosis, an oral agent can have quite prominent glucose-lowering effects, especially when initiated along with lifestyle instruction/modification. The rapid action of the sulfonylureas can help achieve a rapid improvement of glycemic control (30), and the slower onset of action by metformin can similarly lead to an 11–22 mmol/mol (1.0–2.0%) reduction of HbA_{1c}, assisted by reversal of glucose toxicity. As noted above, guidelines generally recommend insulin instead if HbA_{1c} is very high, and this would be particularly true if lifestyle already seemed good or there was suspicion of LADA or pancreatic diabetes (Fig. 1).

In continuing ambulatory care, with established oral therapy, appropriate lifestyle advice will most often already have been given, even if full application of that advice was problematic to the individual. In these circumstances, delaying insulin or other effective therapy while expecting significant further change is unwise. However, when the patient has had limited or no prior education and instruction, further lifestyle counseling in conjunction with even a moderately effective additional therapy can achieve good results.

Otherwise, all oral agents have limited efficacy in the setting of failure of one or more prior oral therapies. The reduction in HbA_{1c} 12 months after supplementing prior oral therapy with a sulfonylurea, metformin, or a thiazolidinedione is no more than 5–11 mmol/mol (0.5–1.0%) from a baseline of ~64 mmol/mol (8.0%), so very few people can be expected to get to target by adding these agents alone (31,32). DPP-4 inhibitors are probably even less effective and SGLT2 blockers no more effective. At higher HbA_{1c}, failure to attain target levels will be inevitable without other change. In all cases, reassessment of glycemic control after 4–6 months is desirable.

GLP-1RAs

An appropriate option to be considered in the ambulatory situation where insulin is also a possible choice is a GLP-1RA. This does not apply to other circumstances where insulin might be started, such as more extreme hyperglycemia, other acute medical illness, or for LADA phenotype or secondary pancreatic diabetes. Advantages compared with insulin might include lack of need for dose titration after the first few weeks, less frequent self-monitoring of glucose, lower risk of hypoglycemia, and a favorable effect on body weight (33). Disadvantages are nausea and sometimes vomiting and other gastrointestinal side effects, as well as uncertainty over increased risk of pancreatitis and indeed other long-term effects. The efficacy of these agents is well documented even when compared with basal insulin treatment, although the insulin doses used in such studies often seem suboptimal (34,35). It is noteworthy that despite frequent reluctance to begin any injected therapy, in both clinical studies and routine practice, insulin is more likely to be continued after initiation than GLP-1RAs.

The GLP-1RA advantage of not being associated with weight gain and very often leading to weight loss is of particular relevance given the frequency of obesity among type 2 patients. Weight gain associated with insulin therapy ranges between 0 and 5 kg in different studies, depending on the baseline HbA_{1c} and the circumstances in which insulin is started (3,7,16). In studies in routine care, the gain of weight is greatest in people who are less obese (36). Although weight gain associated with insulin therapy is widely seen as an argument against using insulin, clear evidence for negative medical outcomes of weight gain is lacking.

Nonetheless, the favorable effect of GLP-1RAs on weight is attractive to providers and patients alike. Preliminary data suggest that this effect is even more apparent for people who have BMI >30.0 kg/m^2 (37,38). Therefore, for an obese person with diabetes not maintaining control targets on lifestyle plus oral agents, the use of a GLP1-RA before introducing insulin therapy may be logical. Obese people on treatment for diabetes are rarely able to fully implement a desirable change of lifestyle, but on occasion, effective weight-reducing therapy can provide a stimulus to further change. However, in general, people with higher HbA_{1c} levels will have less β-cell function, which is needed for GLP-1RA therapy to be fully effective in lowering glucose. Therefore, although glucose reductions are greater with the longer-acting GLP-1RAs (liraglutide and once-weekly exenatide) than with oral agents, it is unreasonable to expect targets to be attained in a majority of people from a baseline HbA_{1c} of >69 mmol/mol (8.5%) unless further lifestyle change is made (33).

Combination therapy of insulin and GLP-1RAs appears effective and may gain the glucose-lowering advantages of both while controlling body weight and reducing risk of hypoglycemia (39). Preliminary evidence suggests that one route to injectable therapy might involve starting the two in combination, even if this means limited titration of insulin doses initially (40). Meanwhile, the addition of either to the other may be clinically advantageous.

Bariatric Surgery

Bariatric surgery has consistently demonstrated significant improvement in blood glucose control compared with standard or intensive medical therapy for people with diabetes, patients with BMI >35.0 kg/m^2, and sometimes the less obese (41–43). Efficacy has been demonstrated across a wide range of age and diabetes duration, comorbidities, or need for current glucose-lowering therapies including insulin. Weight loss after bariatric surgery can be very marked (average of 25 kg or more) and the need for glucose-lowering and blood pressure–lowering medications reduced. However, these procedures appear to be less effective in diabetes when BMI is <35.0 kg/m^2, when the duration of diabetes is >4 years, or when fasting C-peptide levels are

<0.96 nmol/L (<2.9 ng/mL) (44,45). Older people appear likely to have greater risks associated with these surgical procedures (46,47).

This suggests that bariatric procedures deserve consideration for obese but otherwise vigorous people with type 2 diabetes who have disappointing responses to usual glucose-lowering therapies. That bariatric surgery is offered to obese people without diabetes tells us that people with diabetes might benefit if obesity itself is a sufficient indication. For obese people with diabetes already taking insulin, whose continuing weight gain appears to be preventing attainment of glucose control, bariatric surgery may be an option worth considering. However, due to lack of long-term follow-up of outcomes, bariatric surgery does not at the present time seem appropriate as an alternative to insulin and other validated therapies for hyperglycemia but rather as a supplement to them in controlling obesity (48).

A GUIDE FOR THE DECISION TO START INSULIN

Most clinicians do not think algorithmically when managing clinical conditions and advising people with diabetes. They often prefer to follow a patient-led agenda, and individuals will highlight their problems and preferences for solutions in quite different ways. As a result, a simple algorithm for starting insulin is not feasible. However, it is possible to provide a checklist that may help to guide the clinician-patient interaction to ensure that decisions occur in a logical way, and importantly without missing the opportunity to obtain relevant information (Table 2).

The first consideration might be to assess whether an acute need is present, although usually that will be obvious. At diagnosis, other referral, or when admitted for whatever reason as an in-patient, the presence or absence of marked hyperglycemia, weight loss, ketones, ketoacidosis, or dehydration must be ascertained. If marked hyperglycemia alone is present, is there an acute precipitating factor, and if not, is there any prospect that glycemic control can be restored by lifestyle change? Is the patient in a risky or uncertain environment? In these cases, there may be a strong, immediate need, and persuasive advice to consider insulin may be appropriate (Fig. 1).

Then, consider whether the LADA phenotype, pancreatic diabetes, or hepatic cirrhosis may be present. GAD antibody levels may be requested or be available. Deterioration in glucose control over the next 6–24 months despite uptitration of oral agents is perhaps the most important indicator. That should lead to a discussion that insulin therapy is inevitable; in time, it will make management easier and safer.

In longer-term diabetes management, has hyperglycemia progressed rapidly or glucose control been neglected recently? Here the discussion includes alternatives and the likely scenarios for such therapies. This needs discussion of the effects and tolerability of insulin, including hypoglycemia, risks of weight gain, perhaps together with the eventual inevitability of the need for insulin. Whether the introduction of insulin will affect an individual's ability to drive or maintain other key life activities, especially related to occupation, should be explored. Also consider alternatives, including GLP-1RAs, and their attractive features and problems. It is important not to present insulin as indicative of failure or a punishment.

At any stage, the preferred option should be negotiated, with in most cases a contingency planning option if personal targets are not met in a period of months. A further issue here concerns continuing of oral agent therapy, or more specifically sulfonylureas, as metformin is usually continued. If a regimen including mealtime insulin is chosen (including premixes), sulfonylureas are usually stopped to avoid compounding the hypoglycemia risk, but there is less certainty when beginning basal insulin alone where at least temporarily glucose control will deteriorate without rapid insulin dose titration (49). If hypoglycemia does occur on the combination of insulin and a sulfonylurea, clinical experience is that the sulfonylurea should be stopped rather than insulin doses reduced. Thiazolidinediones are also often stopped when starting insulin as the edema and weight gain risks are compounded, but may be worth continuing in the very obese insulin-insensitive individual. A DPP-4 inhibitor can be continued, although perhaps to little benefit.

FURTHER OPTIMIZATION AND PERSONALIZATION OF INSULIN THERAPY

After systematic application of lifestyle, oral agent, and injectable therapies for type 2 diabetes, some patients remain unable to achieve or maintain sufficient glycemic control to avoid the onset or progression of glycemia-related complications. Specifically, even after adoption of initial lifestyle changes, trying adequate courses of oral glucose-lowering agents, starting and optimizing insulin therapy, and consideration of GLP-1RAs, a significant proportion of people have HbA_{1c} levels >53 mmol/mol (7.0%). In the population enrolled in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, which had both 10 years average duration of diabetes and high cardiovascular risk, about 25% of individuals assigned to intensive glucose-lowering therapy were unable to maintain HbA_{1c} levels <52 mmol/mol (7.0%) (50). The further observation that this subgroup, in which insulin therapy was expected to be optimized, had both higher risk of hypoglycemia and higher risk of all-cause mortality has focused attention on the clinical dilemmas posed by such people. A general conclusion is that such people need further consideration of the aims in personalizing their therapy regimens, with the goal of balancing the gains and losses in risk and quality of life from medications. The difficulty in translating this conclusion into practical clinical guidance is well recognized and was reflected by discussions at this expert forum. Several questions were addressed to focus these discussions.

How Can This Category of Patients Be Defined and Identified?

An analysis of data from ACCORD sought to identify baseline characteristics that were associated with excess mortality accompanying intensive as compared with standard treatment. Just three clinical predictors emerged: baseline levels of HbA_{1c} >69 mmol/mol (>8.5%), any prior history of neuropathy, and current aspirin use (51). It is possible the study was too short to have the power to identify other predictors. Poor glycemic control at entry to the study seems likely to have indicated preexisting difficulty with glycemic management, and this in itself may have been associated with

other factors driven out by the multivariable analysis, such as comorbidities. The other "historical" findings (neuropathy and aspirin) imply the presence of already known or suspected complications of diabetes, microvascular and macrovascular. In addition, a subsequent analysis of on-treatment experience in ACCORD indicated that inability to reduce HbA_{1c} by at least by 5 mmol/mol (0.5% units) from the baseline level with an intensive treatment regimen correlated with risk of excess mortality (50). Together these observations suggest that high medical risk (among people already known to have high cardiovascular risk) accompanying intensive therapy can be identified quite early, either by finding poor glycemic control before treatment optimization is attempted or by observing a disappointing response to the first efforts to improve treatment. However, as noted above, many people in poor glucose control have a very good response to insulin therapy, so it is important to distinguish difficulty in obtaining control from neglect of good control. Stated otherwise, people who have little success at first are likely to have difficulty later and are at high risk of diabetes-associated and comorbid adverse outcomes.

Where response to initial insulin therapy is poor, or is initially satisfactory but then deteriorates with time due to progressive islet β-cell failure, the multitude of insulin types do offer various ways to improve clinical results. However, where basal insulin alone is being used, a first action is to ensure the dose has been titrated to usual fasting plasma glucose targets. Use of more extended self-monitoring can then establish the pattern of daytime and nocturnal glucose levels, allowing an informed decision as to the addition of one or more mealtime insulin doses. If simplicity but less flexibility is judged desirable, a switch to premix insulin may be preferred. Coprescription of a GLP-1RA (see GLP-1RAs) is another option.

How Should Glycemic Targets Be Altered?

The simplest and most often discussed modification of usual therapy for people thought to be at high risk is to modify the HbA_{1c} target range. Instead of seeking HbA_{1c} $<$53 mmol/mol ($<$7.0%), higher-risk individuals are commonly advised to aim for between 53 and 64 mmol/mol (7.0 and 8.0%) (23). Although this was the target range for the standard treatment arm in ACCORD, evidence arguing that this range is always the most appropriate remains limited. For example, individuals with limited life expectancy and having HbA_{1c} of 75–86 mmol/mol (9.0–10.0%) probably have little to gain from strenuous efforts to reduce this value to $<$64 mmol/mol (8.0%). Similarly, people with serious medical illnesses requiring complex treatments, such as those with cancer undergoing treatment with cytotoxic regimens, might not need to seek even a relaxed HbA_{1c} target range (23). However, very high HbA_{1c} levels (perhaps $>$86 mmol/mol [$>$10.0%]) are associated with an acute risk of increased infection and vascular thrombosis as noted above (52,53), as well as tiredness, weight loss, and inconvenient polyuria.

How Can Therapeutic Approaches Be Revised?

Even when individuals with conditions or circumstances allowing exemption from specific glycemic targets are removed from discussion, a sizable group of people who have no apparent reason not to attain HbA_{1c} in the 53–64 mmol/mol (7.0 to 8.0%) range remains. Insulin therapy is often said to be unlimited in its capacity to lower glucose levels, but in practice, even very high prescribed doses sometimes yield results that fall short of expectations (54). The underlying causes of failure of usual treatments are undoubtedly numerous, and to understand them calls for further effort to identify the personal characteristics of each person that may prove relevant (Table 3). In many cases, progressive obesity, as a marker for high calorie intake and insulin resistance, identifies a metabolic challenge that resists success even when ample insulin is delivered to tissues. Other medical conditions may be important. Examples include unrecognized Cushing syndrome or a genetic or acquired disorder of extreme insulin resistance.

For some people, psychological factors may interfere with adherence to the regimen or lead to very poor decisions on the timing and dosage of insulin. Obtaining accurate information about actual use of insulin and other medications, independent of what has been prescribed, can be very challenging. For others, environmental pressures, including financial constraints, family or work-related conflict, or social isolation, may prove to be central factors.

Only occasionally will addition of a new medication or change of dosage of existing ones then solve the problem at hand, but consideration of addition of GLP-1RAs, DPP-4 inhibitors, pioglitazone, or SGLT2 blockers is appropriate in some cases (licensed indications vary by market) (39,55,56). In general, all these further lower glucose in the short-term, but this effect may be countered by insulin dose reduction with time. Medications such as GLP-1RAs and SGLT2 blockers can reduce the effects of insulin on weight gain. Pioglitazone can sometimes have dramatic effects on very high insulin dose requirements, but

Table 3—Dealing with problems when on insulin therapy

1. Failure to improve glucose control after adequate dose titration
   - Presence of comorbidities, prior control difficulties, occurrence of hypoglycemia—higher-risk person for amelioration of glucose control targets?
   - Adherence and acceptance of insulin issues?
2. Excessive weight gain
   - Implies high calorie intake—review lifestyle issues and consider a trial of adding GLP1-RA or SGLT2 inhibitor therapy
3. High insulin dose requirement in the markedly obese person
   - Consider trial of adding a thiazolidinedione
4. Severe recurring hypoglycemic events
   - Nocturnal—consider using long-acting insulin analog, timing of basal insulin injection, possibility of hepatic cirrhosis or steroid therapy with need for predominant meal-time insulin therapy
   - Daytime—consider contribution of meal-time insulin (reduce or move to basal-only regimen) or lifestyle issues (missed meals or alcohol)

at the expense of further weight gain. These combinations can be very expensive or of unproven safety and so currently seem appropriate for a minority of insulin takers (57).

When evidence or suspicion of repeated hypoglycemia is present, a change of insulin type or distribution might be beneficial. For people using NPH as basal insulin, the long-acting insulin analogs (glargine, detemir, and degludec) offer evidence-based reduction in risk of nocturnal hypoglycemia (13,14,58,59). For people with daytime hypoglycemia when using sulfonylurea or mealtime insulin together with basal insulin, consideration can be given to reducing the dosage of these agents or stopping them entirely while continuing basal insulin. Substituting a shorter-acting GLP-1RA for mealtime insulin is another option (39). Appropriate lifestyle adjustments to limit hypoglycemia caused by insulin may also be helpful.

Exploring individual factors and their interactions lies at the center of personalized treatment and poses a more difficult challenge in this setting than at the time of starting standard treatments for an unselected population of patients (60). Personalized use of insulin and other therapies by people who have already demonstrated little success with a more generic approach requires time, expertise, and motivation.

SUMMARY AND CONCLUSIONS

The group's discussion noted that insulin has been used longer than any other medication for treating diabetes, and the body of evidence supporting a favorable balance of benefits to risks of its use continues to grow. Some large, long-term clinical trials, including the UKPDS, Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC), and ORIGIN, have shown that both microvascular and cardiovascular benefits can be obtained. Initiation of insulin therapy is appropriate at various stages of diabetes, depending on the clinical circumstances of each case. Use as the first form of pharmacotherapy is needed when the diagnosis of diabetes is made at a time of acute illness or severe metabolic decompensation, or when a form of diabetes characterized by marked insulin deficiency is present. Later, when lifestyle intervention and oral therapies are no longer fully successful, insulin is usually the most desirable first injected therapy, but GLP-1RAs should be considered in some cases because of their unique ability to limit weight gain and reduce glucose with little risk of hypoglycemia. Some large interventional studies, notably ACCORD, suggest that subgroups with less potential benefit and higher risk of hypoglycemia and other complications of insulin use should be identified and managed differently. Although evidence remains incomplete, a history of established complications of diabetes, long-term difficulty with glycemic control, and a poor response to recent efforts to intensify control all argue for adjustment of either the HbA_{1c} target range or therapeutic tactics, or both. Further information on the use of combinations of therapies, especially including the newer agents such as GLP-1RAs, DPP-4 inhibitors, and SGLT2 blockers, for this problematic subgroup of patients is needed. Finally, this discussion clearly demonstrates that despite its long history, much remains to be learned about the best ways to use insulin therapy, which continues to be centrally important in the management of type 2 diabetes.

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