

Insulin therapy in patients with Type 2 diabetes mellitus

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ABSTRACT

Diabetes mellitus is a disease of metabolic dysregulation, most notably abnormal glucose metabolism, accompanied by characteristic long-term complications. The complications that are specific to diabetes include retinopathy, nephropathy, and neuropathy. To achieve glycemic goals in patients with Type 2 diabetes when multiple pharmacologic agents are failing, the early introduction of insulin is key. Our objective is to assist clinicians in designing individualized management plans for insulin therapy in patients with Type 2 diabetes mellitus. We searched Medline, PubMed, journal articles, WHO publications, and reputable textbooks relating to diabetes mellitus and insulin therapy using publications from 1992 to 2016. With the progression of Type 2 diabetes, there is ultimately progressive loss of pancreatic beta-cell function and endogenous insulin secretion. At this stage, most patients require exogenous insulin therapy to achieve optimal glucose control. Choosing from the wide variety of glucose-lowering interventions currently available could be a challenge for the health-care provider and the patients in terms of effectiveness, tolerability, and cost of the various diabetes treatments. However, these should not be the case as risk reductions in long-term complications were related to the levels of glycemic control achieved, rather than to a specific glucose-lowering agent. The challenges of initiating and intensifying insulin therapy are quite enormous and could be daunting to health-care givers. Glycemic treatment should be stepwise with swift introduction of successive interventions after treatment failure (i.e., A1C $\geq 7.0\%$). Insulin should be initiated when A1C is $\geq 7.0\%$ after 2–3 months of dual oral therapy.

Key words: Beta-cell dysfunction, glycemic control, insulin, insulin analogs, Type 2 diabetes mellitus

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INTRODUCTION

Diabetes mellitus is a disease of metabolic dysregulation, most notably abnormal glucose metabolism, accompanied by characteristic long-term complications. The complications that are specific to diabetes include retinopathy, nephropathy, and neuropathy. Patients with all forms of diabetes of sufficient duration, including Type 1 diabetes mellitus (T1DM) and T2DM, are vulnerable to these complications, which cause serious morbidity. These are microvascular complications. High plasma glucose is the driving force in microvascular complications of diabetes.

To achieve glycemic goals in patients with Type 2 diabetes, multiple pharmacologic agents, including sulfonylureas, meglitinides, metformin, alpha-glucosidase inhibitors, thiazolidinediones, dipeptidyl peptidase IV inhibitors, glucagon-like peptide 1 receptor agonist, and insulin, are available. These agents can be used singly or in combination to achieve target glycemic control. Unlike patients with Type 1 diabetes who have no significant insulin secretion and hence require insulin therapy from the onset of their disease, in patients with Type 2 diabetes, insulin resistance with hyperinsulinemia is a prominent feature in the early

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stages of the disease. Patients with T2DM, thus, benefit from measures to improve insulin sensitivity such as dietary caloric restriction, exercise, and weight management early in their disease in combination with oral agents such as insulin sensitizers and insulin secretagogues to achieve the glycemic target. With the progression of Type 2 diabetes, there is ultimately progressive loss of pancreatic beta-cell function and reduction in endogenous insulin secretion. At this stage, most patients require exogenous insulin therapy to achieve optimal glucose control.

Landmark clinical trials have been able to establish the fact that optimal glycemic control can prevent/delay the progression of complications in individuals with diabetes mellitus.^[1] The conclusions from these trials positioned insulin strategically as a very important agent in achieving reduced microvascular complications.^[1,2]

The data from the United Kingdom Prospective Diabetes Study (UKPDS) suggest that early insulin treatment lowers macrovascular risk in T2DM.^[3] These trials strive to achieve glycemic control below which no complication would occur. However, better glycemic control was associated with reduced risks of complications over the whole glycemic range (“the lower the better”) in the UKPDS.^[4]

In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, higher mortality was recorded in the intensive glycemic treatment arm while targeting hemoglobin A1C (HbA1C) of <6.0% compared with the standard therapy group targeting HbA1C from 7.0 to 7.9%.^[5] The intensive arm recorded more episodes of hypoglycemia; hence, the increase in mortality was recorded.^[5] No additional benefit was recorded by lowering HbA1C <6.5% in the KUMAMOTO study.^[2]

Choosing from the wide variety of glucose-lowering interventions currently available could be a challenge for the health-care provider and the patients in terms of effectiveness, tolerability, and cost of the various diabetes treatments. However, these should not be the case as risk reductions in long-term complications were related to the levels of glycemic control achieved, rather than to a specific glucose-lowering agent.^[1] In the Steno-2 study, very few patients achieved the HbA1C target of 6.5% compared with the large number of patients who reached the intensive blood pressure and serum lipid goals.^[6] The challenges of initiating and intensifying insulin therapy are quite enormous and could be daunting to health-care givers. This review contains an overview of the currently available insulin preparations and an outline of the merits and demerits of the various regimens commonly used for the initiation and intensification of insulin therapy in patients with Type 2 diabetes. Understanding that early insulin initiation by the clinician is paramount in order to achieve good glycaemic control and prevent complications resulting from poor glycaemic control in people with type 2

diabetes mellitus. Our aim is to assist clinicians in designing individualized management plans for insulin therapy in patients with T2DM.

RATIONALE FOR INSULIN THERAPY IN TYPE 2 DIABETES

Three major pathophysiologic abnormalities contribute to hyperglycemia in Type 2 diabetes: excessive hepatic glucose production, impaired pancreatic insulin secretion, and peripheral resistance to insulin action occurring principally in liver and muscle tissue.^[1] Of these, peripheral resistance to insulin action and impaired pancreatic beta-cell secretion are early and primary abnormalities, whereas increased hepatic glucose production is a late and secondary manifestation. Early in their disease, patients with Type 2 diabetes compensate for increased insulin resistance at the tissue level by increasing pancreatic beta-cell insulin secretion. When this compensation is no longer adequate to overcome insulin resistance, blood glucose levels begin to rise. Over the course of the disease, however, insulin levels slowly begin to decrease, and eventually, most patients with T2DM are unable to achieve optimal glycemic control with oral agents.^[1] At this stage, the introduction of insulin is inevitable.

HUMAN INSULIN AND ITS ANALOGS

Insulin therapy with 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.^[7] Consequently, treatment with regular insulin is associated with postmeal hyperglycemia and an increased risk of late postprandial hypoglycemia. Second, the conventional basal neutral protamine Hagedorn (NPH) insulin has a distinct peak glucose-lowering effect, has duration of action considerably shorter than 24 h, and is absorbed from the subcutaneous tissue at variable rates. These pharmacodynamics limitations predispose users to elevated glucose levels before breakfast and nocturnal hypoglycemia.^[7,8] 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, and 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. The 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).^[9-11] The pathophysiologic process in T2DM leaves the patient with residual insulin production on the background of insulin resistance. It is worthy to note that

the long-acting insulin analogs have a pharmacokinetics that closely mimics the physiological insulin secretion in the body.

WHEN SHOULD INSULIN THERAPY BE INITIATED?

This question will arise at a point in the management of patients with T2DM, a progressive and chronic disease. The answer is not straight forward. It leaves room for controversy. Oral medications are traditionally introduced in a stepwise manner with insulin reserved as the final step in the management of T2DM. This may take up to 10–15 years after diagnosis before insulin is finally introduced. The fears of painful injections, weight gain, and hypoglycemia militate against early initiation of insulin by both the physician and the patients.^[12-14] Negative beliefs about insulin treatment and other sociocultural factors also affect the acceptance of patients to accept insulin.^[14,15] This predisposes the patient to long-term complications due to exposure to many years of uncontrolled hyperglycemia.^[16] This, therefore, calls for a proactive approach to treatment failure. Lowering glycemia improves insulin resistance as well as insulin secretion.^[17] Early initiation of insulin therapy in a newly diagnosed patient with T2DM restores and maintains beta-cell function.^[17] We advocate that insulin should be initiated when a stepwise approach failed to achieve the target HbA1C of <7%.^[18] This initiation should be swift when the HbA1C <7% is not achieved at 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 the rapid addition of insulin therapy is supported by a numerous studies showing improved treatment satisfaction and quality of life for Type 2 diabetic patients who had started using insulin.^[19,20]

IN WHAT WAY SHOULD INSULIN THERAPY BE INITIATED?

Good glycemic control was achieved in majority of patients with T2DM in the “treat-to-target” clinical trials when basal insulin was added to their oral antidiabetic agents.^[21-23] It should, however, be noted that the benefit of the long-acting insulin analogs is in the reduction of nocturnal hypoglycemia.^[24] According to the ADA (American Diabetes Association)/EASD (European Association for the Study of Diabetes) algorithm for the management of Type 2 diabetes, insulin could be initiated with either once-daily NPH insulin or a long-acting insulin analog.^[18] A meta-analysis that included six randomized control trials comparing NPH and glargine found event rates of 138 and 91 events per 100 patient-years respectively for these

insulins for confirmed symptomatic hypoglycaemia in insulin-naïve type 2 diabetic patients who achieved an A1C of 7.0%.^[25] The NPH, insulin glargine, and detemir have been used as basal insulin to achieve glycemic control in Type 2 diabetes patients. As desirable as this may be, the cost implication of the newer insulin to the patient should not be lost on the physicians. In Africa (and in Nigeria), the cost of insulin has been a barrier to the acceptance of insulin therapy aside from sociocultural issues.^[15] The NPH is cost-effective, and insulin therapy in Type 2 diabetes can be initiated with NPH. Another issue to be considered is the frequency of dosing for basal insulin. In a “treat-to-target” trial with twice-daily detemir administration, an endpoint A1C of 6.8% was reached.^[22] In other studies, a second dose of detemir injection was required in 34–55% of study subjects because of pre-dinner hyperglycaemia.^[23,26] In the only reported trial that investigated the efficacy of once-daily insulin detemir, A1C remained above the currently recommended glycemic goal with an endpoint level of 7.4%, both for NPH insulin and detemir,^[27] compared with an end of study A1C of <7.0% with once-daily glargine and NPH in the original Treat-to-Target Trial.^[21]

In the ACCORD study,^[5] the finding of increased mortality in the intensive glucose-lowering therapy group will probably deter some practitioners from lowering glucose promptly. The ACCORD study solely included patients at high risk for cardiovascular disease, in whom low A1C levels were reached 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%.^[21] An algorithm, which is patient driven, 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.^[28,29] In the timing of once-daily basal insulin regimens, the administration of NPH in the evening appears to be superior to morning injection.^[7,19] There are conflicting results in the studies from studies examining the injection time of the long-acting insulin analogs. When morning and evening injections of insulin glargine were compared in one study, there was a greater reduction in HbA1C and nocturnal hypoglycemia when insulin glargine was given in the morning,^[30] whereas in another larger study with identical design, no significant difference was found in the timing.^[31] 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.^[27] What do all these mean? We can safely conclude from these discrepant data that when nocturnal hypoglycemia limits dose titration of evening detemir or glargine, administration in the morning could be attempted.

Other options exist for initiation of insulin therapy. The treating to target in Type 2 diabetes (4-T) study compared various options of insulin initiation. Basal insulin introduced at bedtime was compared with either biphasic insulin twice daily or prandial insulin before meals.^[26] It was found that regimens using biphasic or prandial insulin reduced HbA1C to a greater extent than basal, but were associated with greater risks of hypoglycemia and more weight gain.^[26] The HbA1C lowering with biphasic insulin is equivalent to prandial insulin. However, there is greater weight gain and more hypoglycemia than with basal insulin, but less for both than with prandial insulin.^[26] Initiation with prandial insulin is not a first-choice approach when initiating insulin in T2DM. Credence was lent to this in the study comparing once-daily insulin glargine versus thrice-daily insulin lispro in insulin-naive patients.^[32] Thus, addition of once daily basal insulin will reduce the frequency of injection and promote acceptability by patients of insulin initiation. Combination of basal insulin with oral agents has been shown to minimize the adverse effects of insulin therapy (i.e., hypoglycemia and weight gain).^[33] Combination of insulin with metformin is indeed associated with better glycemic control, fewer hypoglycemic events, and less weight gain than treatment with insulin alone.^[33] Therefore, metformin should be continued when patients are initiated on insulin therapy (i.e., providing there are no intolerable side effects).

INTENSIFICATION OF INSULIN THERAPY

There is a progressive decline in beta-cell function in T2DM. With the progression, once-daily basal insulin alone will eventually fail to maintain glycemic control in a large number of patients with T2DM. 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 the aggressive titration is limited by hypoglycemia, treatment should be intensified by adding insulin injections. This can be achieved by intensifying the basal insulin or addition of prandial or biphasic insulin. This is individualized based on the patient's diurnal glucose profile. Two 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.^[34,35] 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.^[35] For prandial insulin, rapid-acting insulin analogs are not superior to regular insulin in reducing HbA1C levels or rates for overall and nocturnal hypoglycemia, despite improving postprandial control.^[36] Intensive insulin therapy can also be introduced in patients with T2DM who are already

on at least once-daily insulin injection. Introducing subcutaneous insulin infusion resulted in comparable glycemic control, weight gain, and hypoglycemic risk as multiple daily injection therapy.^[37,38] Multiple daily injection therapy is, however, best administered in selected patients and experienced centers.

DISADVANTAGES OF INSULIN THERAPY

Hypoglycemia is one of the major disadvantages of insulin therapy. Many clinicians are reluctant to initiate insulin therapy for this reason alone. Increased rate of hypoglycemia occurs in intensive glucose-lowering therapy. This was confirmed in the ACCORD study.^[5] Iatrogenic hypoglycemia hampers tight glycemic control and is considered the limiting factor in diabetes management.^[39] In Type 2 diabetes, the frequency of hypoglycemia is generally lower than that in Type 1 diabetes.^[39] 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 counter-regulatory and symptomatic responses to hypoglycemia.^[40]

Weight gain is another disadvantage of insulin therapy. Approximately 2–4-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.^[18,41] Other explanations are snacking to prevent, or in response to, hypoglycemia.

CONCLUSION

Although insulin has no upper dose limit and numerous trials established that glycemic goals can be attained using adequate doses, in clinical practice, many patients experience years of uncontrolled hyperglycemia. Glycemic treatment should be stepwise with swift introduction of successive interventions after treatment failure (i.e., A1C $\geq 7.0\%$). Insulin should be initiated when A1C is $\geq 7.0\%$ after 2–3 months of dual oral therapy. The preferred regimen for insulin initiation in Type 2 diabetes is once-daily basal insulin. For successful insulin therapy, timely initiation and rapid titration are very important. The risk of hypoglycemia is low among Type 2 diabetes patients just commencing insulin therapy. When glycemic goals are not attained despite successful basal insulin dose titration (i.e., fasting plasma glucose ≤ 100 mg/dl) or when the titration is limited by hypoglycemia, treatment should be intensified by the addition of prandial or biphasic insulin.

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Conflicts of interest

There are no conflicts of interest.

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