Over the past decade, eight classes of drugs have been used to treat diabetes; however, insulin remains the most effective and least costly treatment for older adults. The American Diabetes Association has recommended that the approach to drug therapy of diabetes consider insulin a first-tier therapy. Nevertheless, there is a general reluctance among physicians and patients alike to accept insulin. The initiation of insulin therapy is especially challenging in older adults, who often have multiple comorbidities and physical limitations. In this article, we present a case-based approach to the initiation of insulin therapy in older adults.

Key words: diabetes, older adults, insulin therapy, glycemic goals, antihyperglycemic agents

Introduction

Diabetes is a very common condition among older adults.1,2 It is estimated that one in every five people 65 years of age and older have diabetes, and the prevalence of diabetes among older adults is expected to increase by 44% in the next 20 years.3 Older adults newly diagnosed with diabetes experience high rates of complications during the subsequent 10 years, far in excess of those in older people without this diagnosis.4

Over the past decade, eight classes of drugs have been used to treat diabetes: sulphonylureas, biguanides, alpha-glucosidase inhibitors, meglitinides, thiazolidinediones, exenatide, dipeptidyl peptidase IV inhibitors, and pramlintide. However, insulin remains the most effective and least costly treatment for older adults.5 The advent of novel insulin analogues has improved the safety and convenience of insulin therapy.6 However, there is still some controversies on the superiority of insulin analogues over humulin insulin in terms of cost/benefit profile. The American Diabetes Association has recommended that the approach to drug therapy of diabetes consider insulin a first-tier therapy.7 Insulin has no upper dose limit and, unlike other antidiabetic agents, it has no contraindications to its use.8 Nevertheless, there is a general reluctance among physicians and patients alike to accept insulin. The fear of injections, the need for multiple daily glucose tests, and the perceived risks of hypoglycemia have been major deterrents to the widespread acceptance of insulin as first-line therapy (Figure 1). The initiation of insulin therapy is especially challenging in older adults, who often have multiple comorbidities and physical limitations.

How to Decide When to Initiate Insulin Therapy in Older Adults

Case History

A 75-year-old man with history of type 2 diabetes mellitus for the past 8 years presents with a glycated hemoglobin (HbA1c) level of 9.0%, despite taking the maximum effective dosage of metformin and glipizide. He denies any history of coronary artery disease or congestive heart failure. His body mass index is 30 kg/m², and his physical examination is significant for lower extremity edema. His serum creatinine is 141 mmol/L (1.6 mg/dL) and triglyceride level is 5.65 mmol/L (500 mg/dL). What is the most appropriate next step: (1) add pioglitazone; (2) add sitagliptin; (3) add exenatide; (4) add acarbose; (5) add nateglinide; or (6) stop metformin and start insulin?

Should Pioglitazone Be Added?

Pioglitazone is a less attractive option in this case given its low HbA1c-lowering capacity of 0.5–1.4%.9–11 The potential side effects include weight gain, fluid retention, with peripheral edema, and a twofold increased risk of congestive heart failure.12 Moreover, it has the potential to increase the risk of fracture in women and possibly in men.13 The cost of this medication is also a disadvantage.

Should Sitagliptin Be Added?

Sitagliptin is not a good option in this case because of its low efficacy. Its HbA1c-lowering capacity ranges from 0.6 to 0.9%,14,15 The advantages of using this medication in older adults include minimal risk of hypoglycemia, the lack of weight gain, and its utility in chronic kidney disease. On the other hand, the potential of this drug to interfere with immune function, including an increased risk of upper respiratory infection, is of concern.16

Should Exenatide Be Added?

Exenatide has a limited HbA1c-lowering capacity of 0.5–1%.17,18 The cost, the high incidence of nausea associated with its use, its contraindication in chronic kidney disease, the requirement of twice-daily injections, and recent reports of acute
pancreatitis, especially in the presence of high triglyceride levels, make exenatide a poor option for this patient.

**Should Acarbose Be Added?**
Acarbose is a less attractive option in this case given its HbA1c-lowering capacity of 0.5–0.8%. In addition, its cost, gastrointestinal side effects such as flatulence, a contraindication to its use in chronic kidney disease, and the requirement of premeal dosing limit the utility of this agent.

Should Nateglinide Be Added?
Nateglinide, like repaglinide, primarily targets postprandial hyperglycemia. It is not a good option for this patient, who has failed metformin and sulphonylurea combination therapy, and switching or adding a nateglinide will not improve glycemic control. Nateglinide, like sulphonylurea, is associated with a risk of hypoglycemia, weight gain, and a limited HbA1c-lowering capacity of 1.5%, and it is relatively contraindicated in renal failure.

**Should Metformin Be Stopped and Insulin Started?**
Stopping metformin and adding insulin would be the best treatment option for this patient. When a combination of antiglycemic agents fails to optimize blood glucose levels, insulin therapy is usually started. The kinetic profiles of commonly used insulin preparations are summarized in Table 1. Metformin should be stopped when the creatinine level is above 124 mmol/L (1.4 mg/dL) for women or 132 mmol/L (1.5 mg/dL) for men. Metformin is also contraindicated in people over the age of 80. In this age group, if metformin is to be used, creatinine clearance should be measured to verify that it is above 1.336 mL/s (80 mL/min). Glipizide has a relative contraindication in renal failure, and it should be discontinued when creatinine clearance is < 0.501 mL/s (30 mL/min). The major adverse side effect of sulphonylurea is hypoglycemia, which is seen more frequently among older adults. Although sulphonylureas can be stopped once insulin therapy is initiated, it is a common practice to continue sulphonylurea treatment as it may improve postprandial hyperglycemia. In this context, the most common regimen used is referred to as “BIDS” therapy, and it entails bedtime insulin and daytime sulphonylurea use.

Indications to initiate insulin therapy in older adults are presented in Table 2. Table 3 outlines considerations before initiating insulin therapy.

**How to Initiate Insulin Therapy in Older Adults**

**Case History**
The patient described above checks his glucose readings twice a day. His fasting glucose is in the range of 11.1–16.6 mmol/L (200–300 mg/dL), and his daytime glucose is in the range of 5.5–11.1 mmol/L (100–200 mg/dL). What is the optimal choice of therapy at this point: (1) continue glipizide and add basal insulin at bedtime; (2) inject basal insulin in the morning; (3) use premixed insulin twice.
Insulin Therapy in Older Adults
Insulin remains the most effective and least costly treatment for older adults. The American Diabetes Association recommended approach to drug therapy of diabetes considers insulin as a first-tier therapy. Insulin has no upper dose limit and unlike other antidiabetic agents, it has no contraindication to its use.

Insulin helps to deliver glucose to the body by triggering glucose channels in the cell to open. Insulin causes cells in the liver, muscle, and fat tissue cells to take up glucose from the blood, storing it as glycogen in the liver and muscle, and using it as a source of energy. When insulin is absent or in low supply, glucose is not taken up by body cells, and the body begins to use fat as an energy source.
daily with breakfast and supper; or (4) use a combined basal and prandial insulin regimen?

Should Glipizide Be Continued and Basal Insulin Be Added at Bedtime?

A starting dose of intermediate-acting insulin (neutral protamine Hagedorn [NPH] or detemir) or the long-acting insulin glargine at 0.2 U/kg or 10–15 U at bedtime is a reasonable first step for patients with fasting hyperglycemia. The dose is subsequently increased by 1–2 U if fasting blood glucose is not at target on 3 consecutive days. Although a target fasting glucose of 5–6.6 mmol/L (90–120 mg/dL) is reasonable for an older person, this should be individualized depending on the risk of nocturnal hypoglycemia, hypoglycemia unawareness, other comorbidities, and the living situation. If hypoglycemia occurs, or the fasting glucose is below the individualized target range, the bedtime dose should be reduced by 4 U or 10%, whichever is greater. The challenge of starting basal insulin at bedtime is nocturnal hypoglycemia, which is more common among those with type 2 diabetes treated with NPH compared with insulin glargine (28.8% vs. 12.6%, respectively; p = .011).

Should Basal Insulin Be Injected in the Morning?

With fasting hyperglycemia, basal insulin in the morning would not be a first treatment option. However, it is a good option for individuals with daytime hyperglycemia. In addition, if nocturnal hypoglycemia occurs after evening or bedtime administration of insulin glargine, either the dose should be reduced or the timing of the injection should be changed to the morning.

Table 2: Indications for the Initiation of Insulin Therapy in Older Adults

<table>
<thead>
<tr>
<th>Failure of oral antiglycemic agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intolerance to oral antiglycemic agents</td>
</tr>
<tr>
<td>Comorbid conditions that are contraindications to the use of other antiglycemic agents</td>
</tr>
<tr>
<td>Acute illness or perioperative period</td>
</tr>
<tr>
<td>Cost considerations</td>
</tr>
</tbody>
</table>
Should Premixed Insulin Be Used Twice Daily with Breakfast and Supper?
Premixed insulin twice daily with breakfast and supper would be a good option for individuals who have fasting and postprandial hyperglycemia. Glipizide should be stopped when twice-daily premixed insulin is used. Currently, there is no strong rationale to favour bedtime insulin alone or in combination with oral agents over twice-a-day premixed insulin therapy. However, many older adults would prefer to have a once-daily injection than twice-daily injections. Premixed insulin preparations are more convenient and less prone to errors in dosing, but they limit flexibility in diet and lifestyle. The premixed insulin analogues are preferable to premixed human insulin preparations because they can be taken within 15 minutes of a meal and have better postprandial coverage. However, they are more costly.

Premixed insulin therapy is initiated at a dose of 10–12 U administered pre-breakfast and presupper. The presupper dose is titrated on the basis of fasting blood glucose levels, and the prebreakfast dose is titrated on the basis of presupper levels to achieve the target blood glucose value.

Key points regarding the use of premixed insulin are presented in Table 4.

Should a Combined Basal and Prandial Insulin Regimen Be Used?
A combination of long-acting insulin once a day and preprandial rapid-acting insulin is considered an ideal regimen since it mimics basal and prandial endogenous insulin secretion. However, it is a very intense and complex regimen. It may require four to five injections daily and frequent monitoring of blood glucose levels at least three times daily, and it requires special skills in carbohydrate counting and in adding insulin correction doses for preprandial hyperglycemia. Because of the complexity of this regimen, it may not be appealing to older adults.

The initial starting total daily dose of insulin is estimated to be 0.6 U/kg. Approximately half of the total dose should be given as basal long-acting or intermediate-acting insulin, and one-sixth of the total dose (0.1 U/kg per meal) should be given before meals as rapid-acting insulin.

To simplify this regimen for older adults the following is suggested: start bedtime NPH, detemir, or glargine at 10 U or 0.2 U/kg along with 4 U of rapid-acting insulin with each meal. The insulin regimen should subsequently be modified on the basis of the individual’s response to therapy.

Conclusion
Insulin therapy is often combined with oral agents in patients with uncontrolled type 2 diabetes. For practical purposes, the type of insulin regimen is chosen according to blood glucose profiles. The latter can be divided into three general patterns as shown in Figure 2. In addition, special consideration in older adults should be given to their cognitive skills, physical and visual limitations, living situations, available resources, and comorbidities. It is advisable to start slow and to go slowly on insulin titration to avoid hypoglycemia, which usually manifests differently in older adults. Keeping these considerations in mind will enhance the safety and efficacy of insulin therapy in older adults.

Finally, although it may be easier to implement a complex insulin regimen to motivate healthy individuals living in long-term care facilities, it is quite challenging for inactive unhealthy older adults living alone. That is where homecare plays a major role in successful implementation and monitoring of such insulin regimen.

### Table 3: Points to Consider before the Initiation of Insulin Therapy

<table>
<thead>
<tr>
<th>Point to Consider</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Determining the need to start insulin</td>
<td>is not different in older adults than in younger adults.</td>
</tr>
<tr>
<td>Use of different insulin preparations</td>
<td>depends on fasting and daytime blood glucose levels, the patient’s willingness for frequent monitoring of blood glucose, comorbidities, and available resources.</td>
</tr>
<tr>
<td>Patient’s living situation</td>
<td>(alone or with caregiver) and nutritional intake should be considered.</td>
</tr>
<tr>
<td>Visual and physical abilities</td>
<td>are needed to draw up and inject insulin.</td>
</tr>
<tr>
<td>Cognitive skills</td>
<td>are needed to interpret and react to self-monitored glucose readings.</td>
</tr>
<tr>
<td>Individualized glycemic targets</td>
<td>to prevent hypoglycemia must be established.</td>
</tr>
</tbody>
</table>

### Table 4: Usage of Premixed Insulin

Premixed insulin may be used in the following patients:
- Those with hyperglycemia around the clock who are not candidates for multiple daily doses of insulin injection
- Those with persistent hyperglycemia despite being on a combination of bedtime insulin and oral agents
- Those who cannot perform frequent blood glucose monitoring
- Those with a consistent carbohydrate intake who do not miss meals at breakfast and supper

Stop the use of insulin secretagogues such as sulphonylurea and meglitinides when starting prandial or premixed insulin.

Basal/prandial insulin, although complex, allows flexibility in timing and content of meals.
Rational Approach to the Initiation of Insulin Therapy

**Key Points**

- Insulin therapy remains the most effective and least costly treatment regimen for older adults.
- Insulin therapy has no contraindications to its use and no upper dose limit, unlike other antidiabetic agents.
- Hypoglycemia is the most common limiting factor in titrating insulin and usually manifests differently in older adults.
- The type of insulin regimen is chosen according to fasting and daytime blood glucose profiles.
- Home care plays a major role in successful implementation of insulin regimen in older adults.

No competing financial interests declared.

**References**


**Clinical Pearls**

- It is advisable to start low and to go slowly on insulin titration to avoid hypoglycemia.
- When initiating insulin therapy in older adults, special consideration should be given to their cognitive skills, physical and visual limitations, living situations, available resources, and comorbidities.