Insulin use in elderly diabetic patients

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Abstract: The prevalence of type 2 diabetes is increasing among older adults as is their diabetes-related mortality rate. Studies suggest that tighter glucose control reduces complications in elderly patients. However, too low a glycosylated hemoglobin (HbA$_{1c}$) value is associated with increased hypoglycemia. Moreover, the appropriateness of most clinical trial data and standards of care related to diabetes management in elderly patients is questionable given their heterogeneity. Having guidelines to safely achieve glycemic control in elderly patients is crucial. One of the biggest challenges in achieving tighter control is predicting when peak insulin action will occur. The clinician's options have increased with new insulin analogs that physiologically match the insulin peaks of the normal glycemic state, enabling patients to achieve the tighter diabetes control in a potentially safer way. We discuss the function of insulin in managing diabetes and how the new insulin analogs modify that state. We offer some practical considerations for individualizing treatment for elderly patients with diabetes, including how to incorporate these agents into current regimens using several methods to help match carbohydrate intake with insulin requirements. Summarizing guidelines that focus on elderly patients hopefully will help reduce crises and complications in this growing segment of the population.

Keywords: diabetes, insulin, elderly patients

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Introduction

Diabetes mellitus is a major health concern that affects over 150 million adults or 5.4% of the population worldwide; this number will double in the next 25 years (King et al 1998). More specifically, in developed countries defined as Europe, North America, Australia, New Zealand, and Japan, the number of people with diabetes is expected to increase 42% over the next twenty years and in all other developing countries the increase is expected to be 170%. In the US between 1980 and 2003, the number of people with diabetes more than doubled, rising from 5.8 million to 13.8 million (CDC 2005). In 2003, more than 1.3 million adults were diagnosed with diabetes, representing a 52% increase over the number of new cases, 878 000, in 1997 (CDC 2005).

These trends greatly affect the elderly and near elderly as most people with diabetes in the developed world are over 65 years of age, while that of developing countries are 45 to 64 years old. Type 2 diabetes is diagnosed in 10.6% of people over the age of 74 years in the US (NIH 1975). A study reports that one-third of elderly Europeans between age 70 and 75 years have diabetes or impaired fasting glucose (Teuscher et al 1999). The elderly diabetes-related mortality rate is particularly high with 62.3 per 1000 person-years in women and 81.8 per 1000 person-years in men (Bertonia et al 2002).

The American Diabetes Association (ADA) changed their target hemoglobin (A$_{1c}$) level to 7% in recent years based on large, randomized, interventional trials showing that tight glycemic control significantly reduces the risk of developing diabetes complications and, ultimately, the cost of diabetes care (ADA 2005). Studies suggest

that tighter glucose control reduces the chance and severity of stroke, blindness, nephropathy, cardiovascular disease, infections, and even cognitive dysfunction in the elderly (Samos and Roos 1998; CHF/AGSP 2003). It is mindful to consider that a 65 year old now has an 18-year life expectancy that provides time to incur long-term complications (Hogikyan and Halter 1997).

However, too low an A_{1c} value is associated with increased hypoglycemia as a Swedish study noted when an elderly community averaged a glycosylated hemoglobin (HbA$_{1c}$) of 5.9 (Lofgren et al 2004). Of utmost concern in the elderly population is the concern for increased falls with episodes of hypoglycemia creating a cascade of other medical sequela which the patient, family, and provider are anxious to avoid (CHF/AGSP 2003). Thus, hypoglycemia in older adults is a particular challenge for diabetes management because there are increased and unique risk factors (Nettles 2005). Higher risk is associated with the following age-related changes: decreased renal function, slowed hormonal regulation and counter-regulation, suboptimal hydration, and slowed intestinal functioning (absorption). The increased likelihood of older adults being on multiple medications and exhibiting inadequate and/or erratic nutritional intake introduces factors that put them at higher risk for hypoglycemia. At the same time, it is also important to note that older adults are at increased risk for having hyper and hypoglycemic symptoms misattributed to other factors such as other comorbid conditions, side effects from medications, or the aging process itself.

One of the biggest struggles for clinicians in achieving tight control while preventing hypoglycemia in their elderly patients is to predict when peak insulin action will occur. This depends not only on the patient's carbohydrate intake and absorption, but on their activity level as well. Miscalculating an elderly patient's insulin requirements may lead to a sharp, severe lowering of blood glucose, necessitating emergency treatment (Watts and Ober 2005).

The clinicians' options for safe insulin regimens in the geriatric population have expanded greatly in the last 10 years. It now includes several insulin analogs: these are synthesized drugs that have a modified pharmacokinetic profile by altering the amino acid sequence of natural insulin (Engel et al 2004a, 2004b). These analogs show great promise to help patients lower their blood glucose to levels because their pharmacokinetics nearly mimic the physiology of the nondiabetic state (Mudaliar et al 1999; Lepore et al 2000; Bode 2004). These new insulin analogs

physiologically match the insulin peaks of the normal glycemic state, enabling patients to achieve the tighter diabetes control in potentially a safer way.

Glycemic control does not happen in a vacuum and this is particularly true for older adults. The heterogeneity in clinical and functional status among elderly patients has important ramifications for the management of diabetes. Elderly patients with diabetes are disproportionately affected by other health conditions and adverse outcomes such as cognitive impairment, limitations in functional status, depressive symptoms, heart disease, and stroke (Blaum et al 2003; CHF/AGSP 2003; ADA 2005; Nettles 2005). The potential costs in terms of morbidity are particularly salient in light of the consideration that a recent study found that the majority of their sample of older patients with type 2 diabetes indicated that a primary health goal was maintaining independence in daily living (Huang et al 2005). The clinician must weigh many factors as the risks and benefits of tight glycemic control in elderly patients are evaluated in the context of treatment strategies and priorities.

Thus, while some have endorsed lowering the goal of HbA$_{1c}$ levels to less than or equal to 7.0%, the importance of tailoring or individualizing the target level is often acknowledged when applying this recommendation to an elderly population (eg, CHF/AGSP 2003). At the same time this introduces controversy and a lack of consensus about managing diabetes in elderly patients. This is due in part to the complexity and heterogeneity of their clinical and functional status and currently having no studies that address the longer-term benefits and risks associated with tight glycemic control in older adults (ADA 2005). Insulin analogs are available now to help the clinician manage diabetes in such a complex and heterogeneous population but it is critical to understand the risk and benefits of these analogs.

We will discuss the function of insulin in managing diabetes and consider how the newer insulin analogs assist with the overall goal of providing optimum diabetes disease management with a focus on the special concerns when treating elderly patients. Specifically, we will review what factors clinicians should consider when revising a patient's insulin regimen to include these analogs and suggest several methods, including correction factors, by which appropriate dosages may be deduced. The insulin treatment guidelines summarized and presented with elderly patients in mind hopefully will help to reduce crises and complications in this growing segment of the population and provide safe options for individualizing treatment.

Insulin's pathophysiology and management of diabetes

The pancreas produces a constant, or basal, production and circulation of insulin, which regulates the output of hepatic glucose (maintaining blood levels above 60 mg/dL) and modulates muscle and other tissue uptake. Additionally, a physiologic bolus of insulin is secreted at mealtimes in proportion with the carbohydrate intake. This helps the body utilize this energy source for metabolism.

Glucose lowering agents are often necessary to help patients with diabetes achieve the tight glucose control that their pancreas cannot achieve. Patients with type 1 diabetes require insulin injections because of a complete lack of endogenous insulin; however patients with type 2 diabetes may achieve glycemic control through oral medications. A common scenario occurs when oral therapy no longer maintains blood glucose within generally accepted targets and injected insulin may then need to be added to the regimen. However, oral glucose lowering agents should not necessarily be discontinued at this time. Indeed, these can work synergistically with insulin to make the regimen more effective (Wright et al 2002).

There are no clinical guidelines when to intensify medical therapy in the elderly. Each patient must be treated individually. However, if the fasting plasma glucose is roughly 200 mg/dL despite maximal oral glucose lowering agents, then prandial values exceed this number with the resultant potential for significant hyperglycemia, and an injectable agent should be considered (Saudek and Golden 1999).

Historical insulin effects

The regular human insulins were the only formulations available during the past decades to provide patients with the necessary preprandial bolus doses. Regular insulin's onset of action begins in 30 minutes to one hour (Table 1) (Dailey 2004; Engel et al 2004b; Drug Guide 2005) and reaches peak serum concentrations corresponding to peak action in about two to four hours (Dailey 2004). This delayed onset means the patient must carefully plan mealtimes to avoid hypoglycemia and doesn't allow for too much variance such as skipping a meal or overeating.

Historically, basal insulin was provided through various regimens using either intermediate-acting neutral protamine Hagedorn (NPH) insulin, insulin lente, or long-acting ultralente insulin. NPH insulin has the earliest onset of action beginning in two hours (Engel et al 2004b). Peak serum

Table 1 Pharmacodynamics of human insulin and insulin analogs[1]

Insulin type	Time to onset of action (h)	Time to peak action (h)	Duration of action (h)
Human insulin			
Rapid-acting			
• Regular insulin	0.5–1	2–4	6–8
Intermediate-acting			
• NPH insulin	2–4	5–7	14–24
• Insulin lente	3–4	4–8	16–20
Long-acting			
• Ultralente insulin	6–10	Unpredictable	20–24
Insulin analogs			
Rapid-acting			
• Insulin lispro	0.25	1.5	3–5
• Insulin aspart	0.25	1.5	3–5
• Insulin glulisine	0.25	1	2
Long-acting			
• Insulin glargine	2–4	Peakless	20–24

[1]Wide variations occur among patients. (Bode 2004; Engel et al 2004; Watts and Kern 2004; Watts and Ober 2005).
Abbreviations: NPH, neutral protamine Hagedorn.

concentrations are variable with five to seven hours for NPH insulin, four to eight hours for insulin lente, or unpredictable for ultralente (Dailey 2004). The latter two insulins are currently being phased out in formularies in the US (Fleming 2005).

The rapid-acting insulin analogs, insulin lispro and insulin aspart, as well as the long-acting analog, insulin glargine, have added a new facet to diabetes therapy with improved onset and peak concentration times. Due to their smooth action and predictability, these insulins offer an ideal match with the elderly population to avoid hypoglycemia.

New insulin analogs

Three rapid acting insulin analogs have been introduced in the last nine years. The insulins lispro and aspart were brought to the US market in 1996 and 1999, respectively, and in April 2004, the US Food and Drug Administration (FDA) approved a third rapid-acting analog, Insulin glulisine (Thompson 2004). The insulins lispro and aspart achieve peak concentration within 90 minutes and have a duration of action of approximately three to five hours (Bode 2004), while glulisine's peak concentration is within an hour, and its duration of action is roughly two hours (Drug Guide 2005). All three of these rapid-acting analogs have an onset of action within 15 minutes. This rapid onset of action means that the patient can now pair the dose of insulin injected to the amount of carbohydrate consumed. Timing slightly

varies among the insulins: insulin lispro can be taken up to 15 minutes before a meal or immediately after a meal, insulin aspart immediately or within 10 minutes of starting a meal, and insulin glulisine up to 15 minutes prior to or 20 minutes of starting a meal (Drug Guide 2005). Elderly patients with renal insufficiency may benefit from the quick action of lispro and experience less hypoglycemic episodes (Velussi 2002).

Hypoglycemia is a dangerous complication of all types of insulin and patients should be cautioned not to administer any of the rapid-acting analogs at bedtime. These analogs are solely to be used for mealtime insulin coverage and, if administered at bedtime, can cause glucose levels to drop severely during sleep. For those patients who just can't seem to resist constant evening snacking on carbohydrates, regular insulin, which has a longer time to peak concentration and a longer duration of action, may provide a longer duration of blood glucose lowering (Watts and Ober 2005). As such, it is critical to understand each elderly patient's meal and snacking preferences and habits.

Elderly patients and their families need to understand the time course of these new insulins. We have seen patients who believe they can inject a rapid-acting analog at home and then go to a restaurant and order a meal, a practice similar to bedtime administration, which causes potentially life-threatening episodes of hypoglycemia. Patient and family education cannot be over-emphasized as in one study nearly 32% of elderly patients receiving insulin had no knowledge regarding hypoglycemia (Thomson et al 1991).

Insulin glargine

Initially introduced in 2001, insulin glargine has been touted as the first major advancement in the treatment of type 1 and type 2 diabetes in over 50 years (Home and Ashwell 2002). This analog delivers a basal insulin delivery that has no significant peak, and can be administered at nearly any time of the day, be it morning, noon, or evening, provided that the patient consistently administers it at the same time each day.

The time to onset of action is two to four hours and total duration of action is about 20 to 24 hours (Bode 2004). There is a lower incidence of associated symptomatic hypoglycemia and nocturnal hypoglycemia in type 1 and type 2 diabetes when compared with NPH insulin (Ratner et al 2000; Yki-Jarvinen et al 2000; Rosenstock et al 2001). However, insulin glargine cannot be mixed with any other insulins due to its acidic pH.

The glargine package insert suggests reducing the dosage by 20% when converting from other basal insulins to insulin glargine – especially if the patient has type 1 diabetes. The peakless insulin glargine is likely to provide tighter blood glucose control than the older basal insulins, which produce peak concentration levels requiring patients to self-treat episodes of hypoglycemia with carbohydrate snacks and ultimately administering additional insulin to compensate for the resulting hyperglycemia (Janka et al 2005). Such a risky adjustment cycle is of particular concern among elderly patients and emphasizes the importance of education to achieve tighter and safer glucose control.

Insulin therapy in patients with type 1 diabetes usually is initiated at a total daily dosage (TDD) of 0.3 IU/kg to 0.8 IU/kg per day (APA 2001). In patients with moderate type 2 diabetes (defined as a fasting blood glucose between 140–250 mg/dL), the patient's TDD of insulin usually ranges from 0.3 IU/kg to 0.6 IU/kg (APA 2001; ADA 2002).

After the correct TDD of insulin is determined, patients with type 1 diabetes may take half that amount in the form of basal insulin and half in the form of rapid-acting insulin, the latter is equally divided between three mealtime bolus doses in basic proportion to the amount of carbohydrates consumed.

A strategy in patients with type 2 diabetes is to directly switch from NPH insulin-to-insulin glargine, using glargine at the same dosage as was used for NPH. The caveat is that the patient has not experienced any recent episodes of hypoglycemia.

It is important to monitor both fasting and preprandial blood glucose levels in order to assess therapeutic efficacy by comparing them with the American Diabetics Association (ADA)'s ideal levels, which are 90–130 mg/dl (ADA 2005). Such comparisons can be used to modify therapy (Table 2) (Watts and Kern 2004) and while of general application the ADA levels are useful guidelines for elderly patients and their families.

Table 2 Blood glucose levels indicating excessive circulating insulin[1]

Blood glucose levels (mg/dL)			
Fasting	Pre-lunch	Pre-dinner	Bedtime
78	60	55	89
111	70	65	109
65	55	68	106

[1]Patient presenting with such blood glucose readings would be advised to reduce basal insulin by 10% to 20% and to monitor blood glucose levels closely for three to four days afterward to determine whether the change has been effective (Watts and Kern 2004; Watts and Ober 2005).

Calculating mealtime carbohydrates

The best method to calculate mealtime insulin is to directly match the amount of insulin to the expected amount of carbohydrates to be consumed. This requires some sophistication as well as a genuine effort made by the patient.

Patients with type 1 diabetes, generally start with dosing 1 IU preprandial, rapid-acting insulin for every serving (15 g) of carbohydrate consumed. For patients with type 2 diabetes, the optimal dose of rapid-acting insulin widely varies due to insulin resistance.

Such factors in these patients that contribute to the difficulty of making a standardized calculation include the duration and progression of the diabetes, the patient's body mass index, and genetic factors. However, several methods are available for roughly estimating the approximate coverage required (Table 3) (Watts and Ober 2005). Having several methods permits finding a method that best matches the individual preferences of and differences among elderly patients.

Method 1: The 500 rule

Patients with good glycemic control, as evidenced by A_{1c} levels of 7.0% or lower, can determine their insulin-to-carbohydrate ratio by dividing 500 by their TDD of insulin (basal + bolus in IU) (Walsh and Roberts 2000). This approximates the number of carbohydrate grams that 1 IU insulin covers. Extremely insulin-resistant patients may use a TDD of 100 IU insulin; the insulin-to-carbohydrate ratio would be 1:5, meaning that 1 IU insulin can be expected to provide coverage for 5 g carbohydrate ($500 \div 100 = 5$), or

about one third of a piece of bread. A patient with a TDD of only 20 IU insulin would divide 500 by 20 and arrive at an insulin-to-carbohydrate ratio of 1:25. For this patient, 1 IU insulin provides coverage for 25 g carbohydrate.

Method 2: The conventional formula

A second common method to determine the amount of rapid-acting insulin needed for preprandial coverage is to use the convention 1 IU per 15 g carbohydrate consumed. For example, if a patient's planned meal contains approximately 60 g carbohydrates, then 4 IU rapid-acting insulin ($60 g \div 15 g = 4$ IU) is required to provide coverage for the meal. Clinicians must note that this method requires checking both preprandial and two-hour postprandial glucose levels to verify accuracy of dosing. If preprandial blood glucose values are within target range and postprandial levels are elevated no more than 40 mg/dL above preprandial levels, then the provided bolus dose is sufficient. If postprandial levels are lower than the preprandial levels, then the scheduled dose was excessive and hypoglycemia could ensue.

Method 3: Using body weight

A third formula for calculating the insulin-to-carbohydrate ratio often is recommended for patients with type 1 diabetes: [2.8 x (body weight in lbs)] ÷ TDD of insulin (in IU) (Bode 2004). In following this formula, a patient weighing 200 lbs whose TTD of insulin was 50 IU, would take 1 IU preprandial insulin for every 11 g carbohydrate consumed ([2.8 x 200 lbs] ÷ 50 IU = 11.2).

Table 3 Summary chart for methods of calculating insulin and caveats for older patients

Method	Approach	Caveats
Method 1: 500 rule	$\dfrac{500}{\text{TDD of insulin (basal + bolus in IU)}}$	
Method 2: Conventional formula	1 IU per 15 g carbohydrate consumed	If postprandial levels are lower than preprandial levels, hypoglycemia may result
Method 3: Using body weight	$\dfrac{[2.8 \times (\text{body weight in lbs})]}{\text{TDD of insulin (in IU)}}$	Recommended for type 1
Method 4: No-count approach	Small preprandial dose: 2–4 IU*	1. *Factor in weight, type of diabetes and typical meal 2. Check pre and post-prandial levels regularly 3. Correction factor helpful
CF	1700/TDD (in IU)	Patients must not use this at bedtime

Abbreviations: CF, correction factor; TDD, total daily dosage of insulin in IU.

Method 4: The no-count approach

For patients unable or unwilling to learn carbohydrate counting, a small dose (2–4 IU, depending on weight, type of diabetes, and typical meals) of preprandial insulin can be prescribed. Advise these patients to check preprandial and 2-hr postprandial glucose levels regularly to determine the accuracy of the dosing. In addition, a correction factor may also benefit these patients.

Correction factors

There will be occasions, due to stress or overeating, when blood glucose levels will rise, despite the clinician's and patient's best efforts to calculate correct dosages. It is helpful if elderly patients and their families know a correction factor for these occasions so that they can adjust his or her insulin dose accordingly.

If A_{1c} levels are 7.0% or lower, the following formula may be used to calculate the glucose correction factor (CF): $1700 \div TDD$ (in IU) = CF, where CF represents the degree to which 1 IU insulin is expected to lower the patient's blood glucose (in mg/dL) (Bode 2004). Therefore, if the patient is on a TDD of 34 IU and taking a bolus analog insulin then their CF would be 1700/34 meaning 1 unit of insulin will bring their blood glucose down by about 50 points. Therefore, if their blood glucose is 180 mg/dL before a meal you would add 1 additional unit as a correction factor to their mealtime insulin to correct this high blood glucose.

It is important to caution elderly patients and their families not to use this correction factor at bedtime because rapid-acting insulin analogs are associated with peak concentration levels and may result in nocturnal hypoglycemia. If blood glucose levels are elevated before a patient goes to bed, advise the patient and their family to make a correction the following morning.

Summary: a delicate balance and challenge – achieving the goal of tighter glucose control in elderly patients

Although many insulin-based regimens have been used safely in elderly patients (Elgrabley et al 1991; Miles et al 1994), hypoglycemia is a concern and challenge for obtaining tighter glycemic control, as mentioned. Known risk factors for severe hypoglycemia in the elderly are recent hospital discharge, advanced age, and polypharmacy or the use of 5 or more prescribed medications (Shorr et al 1997). Putative mechanisms for this include an age-associated decrease in hepatic oxidative enzyme activity and concomitant decline in renal function (Chelliah and Burge 2004). In addition, elderly patients, particularly those who have had diabetes for many years, may lose epinephrine and glucagons responses to hypoglycemia, leading to a lack of awareness from loss of warning symptoms (Benbarka et al 1998).

Strategies to prevent this include educating the patient, family, and close friends to recognize the signs and symptoms of hypoglycemia, performing regular home blood glucose monitoring, and practicing safe driving (Chelliah and Burge 2004). It is important to advise patients to carry a replacement glucose source in the pocket, purse, bedside stand, and car. Additionally, many patients are unaware of the blood glucose-lowering effect of alcohol and need to be counseled about moderation and to ingest more carbohydrates if they are going to imbibe.

Caring for elderly patients with diabetes necessitates acknowledging the variability and complexity of this population. As such, the target hemoglobin should always be a reasonable goal that considers the patient's status with regard to clinical issues and physical, emotional and cognitive functioning including consideration of life expectancy (Blaum 2002; CHF 2003). While a goal of 7% or lower may be appropriate for some older adults who are healthy, such a target value for other older adults may be inappropriate. Similarly, the establishment and prioritizing of treatment goals needs to consider other common syndromes in elderly patients with diabetes, such as depression, injurious falls, and cognitive impairment. It is important that clinicians continually reassess the patient's status and circumstances. It is worth informing patients and families that self-management training and classes are available and may be covered by insurance plans (for example, annual training is covered under Medicare in the US) (CHF 2003).

In summary, these new insulin analogs have created another tool to enable the clinician to help their elderly patients achieve consistent, well-defined glycemic control. Although a strategy of basal-bolus insulin therapy using these analogs lowers the incidence of hypoglycemia among patients with diabetes, the clinician should remain ever vigilant to this risk, especially in elderly patients. The formulas presented serve as a guideline to help estimate a patient's insulin requirements, however it is important to remember that all insulin titration must reflect the patient's unique characteristics to achieve ideal results and be routinely monitored within the context of regular and thorough geriatric assessments.

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