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Focus on Insulin's History and the Persistence of Sliding Scale

By Allen Lefkovitz

Insulin is a hormone produced and released by beta cells of the pancreatic islet cells, and it controls the body's use and storage of the glucose obtained from food. Nearly 100 years ago, insulin became one of the greatest medical breakthroughs in history. On January 11, 1922, Leonard Thompson, a 14 year-old boy with type 1 diabetes mellitus (DM) in a Toronto hospital, became the first person to receive an insulin injection. Although his first insulin injection resulted in an infection at the injection site and only a slight reduction in blood glucose, 12 days later a further refined insulin product was given which normalized his blood glucose. While not a cure for DM, the discovery of insulin led not only to the Nobel Prize in Physiology or Medicine for 1923 but also to countless lives saved over the past century.

Since the 1920's several advancements in insulin therapy have occurred including:

1946	• Extended-action, twice-daily NPH (neutral protamine Hagedorn) insulin became available
1982	• The concept of "basal-bolus" insulin therapy was introduced
1982	• The FDA approves regular and NPH insulins manufactured using recombinant DNA technology, eliminating the need for animal-based insulins
1985	• Insulin pen delivery system introduced
1996	• The first insulin analog [Humalog (insulin lispro)] was approved • Analogs are made by small modifications to insulin's structure to further optimize insulin's absorption, distribution, or metabolism
2000	• The first basal insulin [Lantus (insulin glargine)] was approved, allowing for once daily administration due to its longer duration of action
2006	• The first inhaled insulin (Exubera) approved but was discontinued in 2007 – 2014 – a second inhaled rapid-acting insulin product (Afrezza) approved
2015	• Two concentrated insulins were approved by the FDA [i.e., insulin degludec (Tresiba U-200), and insulin glargine (Toujeo U-300)]
2021	• The FDA approves the first interchangeable biosimilar insulin product [Semglee (insulin glargine-yfgn)]

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Within long-term care (LTC), four of the most common types of insulin regimens are:

Basal insulin – use of a longer acting insulin intended to mimic the physiologic, slow, and steady release of insulin	**Bolus insulin** (also called prandial or mealtime insulin) – scheduled short- or rapid-acting insulin specifically intended to help address food consumption
Sliding Scale insulin (SSI) – use of an as needed short- or rapid-acting insulin based upon an elevated blood glucose often before meals and at bedtime Defined by the ADA as "short- or rapid-acting insulin coverage only with no basal insulin dosing"	**Correction-dose/Supplemental insulin** – appears similar to SSI but is a) not used by itself and b) is individualized to the person's total daily insulin needs and/or their meal intake

ADA: American Diabetes Association

The Persistence of Sliding Scale Insulin

SSI is considered to be one of the most commonly utilized insulin regimens in LTC. SSI was first described in 1934 by Dr. Elliot Joslin, considered the father of modern-day diabetes care. Originally based upon color-coded urine glucose testing, when capillary blood glucose monitoring became more readily available in the 1970's and 1980's, SSI became a means of providing as needed insulin based upon pre-meal or bedtime blood glucose concentrations. Yet numerous articles dating as far back as 1963 have questioned the value of chronic SSI administration. As such, SSI is considered by some to be an insulin-related discovery in the past 100 years that has persisted too long.

Reasons where temporary use of SSI is more likely to be considered include:

- during short-term acute illness when blood glucose may fluctuate dramatically;
- following a new diagnosis of type 2 DM when insulin requirements are initially unknown;
- when enteral or parenteral nutrition is necessary; and
- when corticosteroids (e.g., prednisone, methylprednisolone) must be initiated.

However, numerous concerns with its chronic use include that SSI:

- is a reactive approach instead of a preventative approach;
- involves an increased number of injections and increased blood glucose monitoring, both of which lead to greater discomfort and increased nursing time;
- can lead to rapid changes in blood glucose exacerbating both hyperglycemia and hypoglycemia;
- wrongly assumes all individuals have similar insulin sensitivities or no change in insulin sensitivity during different stages of acute illness;
- promotes a misconception that mild elevations in glucose (e.g., < 200 mg/dL) are harmless;
- usually provides only minimal amounts of insulin coverage for a meal itself, which subsequently results in continued hyperglycemia; and
- orders are less likely to be changed ("therapeutic inertia") and are therefore not individualized to a resident's needs.

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Notwithstanding these concerns, recent literature has suggested that SSI persists:

- A 2017 Cleveland Clinic study examining 200 residents with DM discharged to a LTC facility from the hospital found that 74% had regimens that included SSI and 25% received only SSI.
- A 2021 Veterans Affairs exploratory chart review of 49 nursing home residents receiving a short-acting insulin found that 61% were admitted on SSI.
- A May 2021 systematic review in the Journal of the American Medical Directors Association (JAMDA) reported on three studies that showed a 24% to 56% prevalence of SSI in LTC. Within this JAMDA systematic review, one study found that "37.7% of residents with T2DM received SSI and the same residents were involved in 50% of major hypoglycemic episodes and 50% of all minor hypoglycemic episodes."

Several guidelines and organizations promote individualization of diabetes care and recommend avoiding use of SSI as a primary means of regulating blood glucose.

- Since 2012, SSI has been included in the American Geriatrics Society Beers Criteria®. The latest 2019 Criteria recommend avoiding the use of SSI and define SSI as "insulin regimens containing only short- or rapid-acting insulin dosed according to current blood glucose levels without concurrent use of basal or long-acting insulin." SSI is included because of "Higher risk of hypoglycemia without improvement in hyperglycemia management regardless of care setting."
- Within their 2013 Choosing Wisely® document, the Society for Post-Acute and Long-Term Care Medicine recommended against the use of SSI "for long-term diabetes management for individuals residing in the nursing home" because "Good evidence exists that SSI is neither effective in meeting the body's physiologic insulin needs nor is it efficient in the long-term care (LTC) setting in medically stable individuals."
- The 2021 ADA Standards of Medical Care in Diabetes only discuss SSI within the context of the inpatient hospital and "strongly" discourage use as "basal-bolus treatment improved glycemic control and reduced hospital complications compared with reactive, or sliding scale, insulin regimens".

Despite the abundance of literature opposed to SSI, very little guidance exists on specific strategies to eliminate SSI once it has been initiated. Ideally, use of SSI should be re-evaluated within 7 to 14 days after initiation of or admission on SSI. Beyond optimizing the use of other non-insulin antidiabetic therapies (e.g., metformin), the "Management of Diabetes in Long-term Care and Skilled Nursing Facilities" ADA position statement provides several strategies, including but not limited to:

- Discontinuing SSI when blood glucose stabilizes, and coverage is unnecessary most days of the week.
- Reviewing the average daily insulin requirement over the prior 5 to 7 days and giving 50 to 75% of the average daily insulin requirement as basal insulin, while using non-insulin agents or fixed-dose mealtime bolus insulin for postprandial hyperglycemia.
- If they are receiving SSI and basal insulin, adding 50-75% of the average insulin SSI requirements to the existing basal insulin dose and using non-insulin agents or fixed-dose mealtime insulin for postprandial hyperglycemia.

As always, glucose monitoring should continue following any change in antidiabetic therapy. In addition to improving quality of life and improving overall glycemic control, minimizing the use of SSI may also be seen as fulfilling the ADA Standards call to achieve drug regimen simplification thereby requiring fewer administration times, fewer blood glucose checks, and fewer calculations.

New Generic Medications

By Allen Lefkovitz

Generic Name	Brand Name	Date Generic Available
Fenofibrate Micronized 30 mg and 90 mg Capsule	Antara® Capsule	11/2/21
Varenicline 0.5 mg and 1 mg Tablet	Chantix® Tablet	10/4/21
Everolimus 10 mg Tablet	Afinitor® Tablet	10/4/21
Everolimus 2 mg, 3 mg, and 5 mg Tablet for Suspension	Afinitor Disperz® Tablet for Oral Suspension	10/4/21
Nebivolol 2.5 mg, 5 mg, 10 mg, and 20 mg Tablet	Bystolic® Tablet	9/20/21
Difluprednate 0.05% Ophthalmic Emulsion	Durezol® 0.05% Ophthalmic Emulsion	9/17/21
Paroxetine 10 mg/5 mL Oral Suspension	Paxil® Oral Suspension	9/17/21

New Drug

By Dave Pregizer

Kerendia® Tablet

Brand Name (Generic Name)	Kerendia ® [ker-EN-di-a] (finerenone) [fin-ER-e-none]
How Supplied	10 mg and 20 mg tablets
Therapeutic Class	Non-steroidal mineralocorticoid receptor antagonist (MRA)
Approved Indication	To reduce the risk of sustained eGFR decline, ESKD, cardiovascular death, non-fatal myocardial infarction, and hospitalization for heart failure in adults with CKD associated with type 2 diabetes
Usual Dosing	Starting dose: 10 mg or 20 mg orally once daily with or without food, based on eGFR and K^+. Increase dose after 4 weeks to the target dose of 20 mg once daily, based on eGFR and K^+ thresholds. May be crushed.
Select Drug Interactions	Strong CYP3A4 inhibitors (e.g., clarithromycin) are contraindicated. Avoid concomitant use with a strong or moderate CYP3A4 inducers (e.g., carbamazepine) or grapefruit or grapefruit juice. With moderate or weak CYP3A4 inhibitors (e.g., diltiazem, cimetidine), monitor K^+ during drug initiation or dose adjustment of either Kerendia or the interacting drug.
Most Common Side Effects	Hyperkalemia, hypotension, and hyponatremia
Miscellaneous	Measure K^+ and eGFR before initiation. Do not start treatment if K^+> 5.0mEq/L. Adjust dose according to K^+ 4 weeks after start, then periodically.
Website	http://Kerendia.com

CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; ESKD: end stage kidney disease; K^+: serum potassium