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UPDATE IN INSULIN THERAPIES



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OBJECTIVES

- * Review insulin preparations, types of delivery and their pharmacokinetics as determinants for designing an insulin regimen.
- * Discuss and compare available formulations of insulin, including the newest types and those to be approved in the near future.

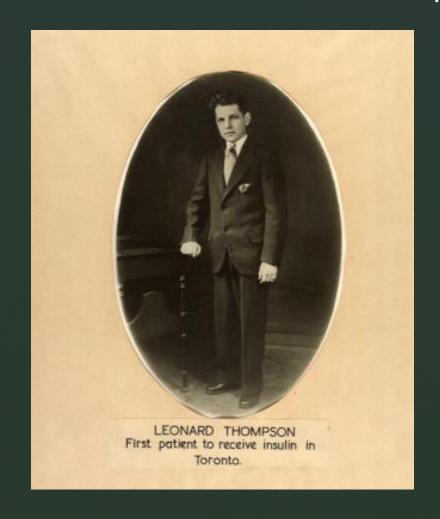






- In 1921, Macleod (physiology professor in Univ of Toronto) accepted a proposal by Frederick G. Banting, a 22-year-old physician and surgeon, to work in his laboratory to test his ideas on pancreatic extracts for reducing blood glucose in diabetic dogs.
- Banting, assisted by summer student Charles Best, began to accumulate evidence that these extracts worked.
- Collip, a visiting biochemist, joined the group and provided the expertise needed to purify the active glucose-lowering component from the extracts.
- Key developments from other labs and the pharmaceutical industry allowed for the large-scale commercial production of insulin by the end of 1923.

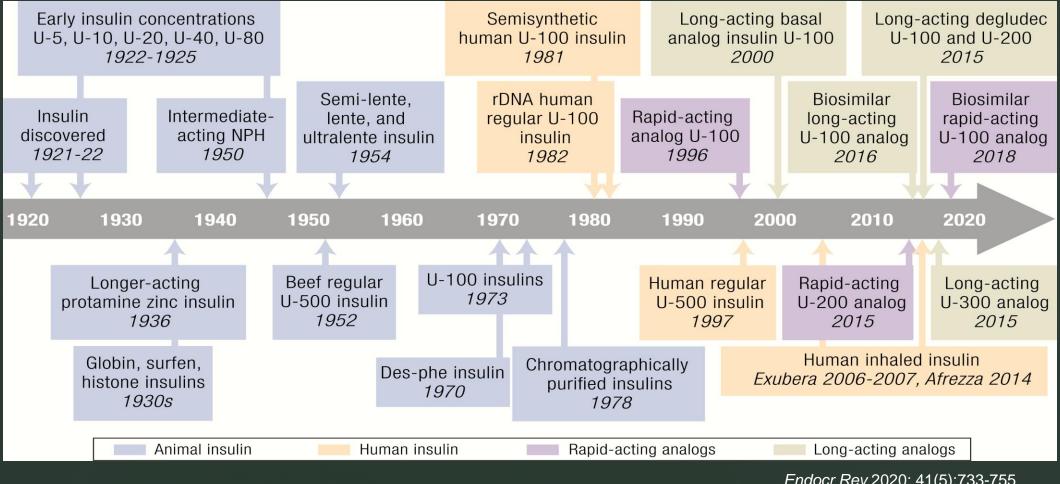
On January 23, 1922, 14-year-old Leonard Thompson became the **first** person to receive an **insulin** injection as treatment for diabetes extracted from cattle pancreas.



The first commercial insulins were impure, large-volume bovine or porcine formulations injected with large needles that patients had to sharpen themselves.







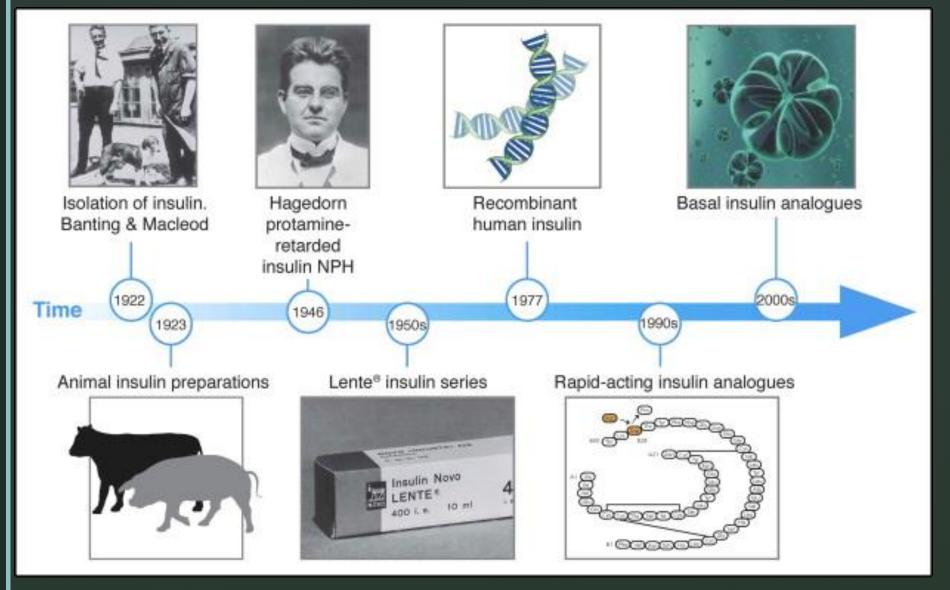
Endocr Rev 2020; 41(5):733-755

The first commercial insulin formulations were made with beef and pork insulins due to their similar PK and PD properties to human insulin, but caused the generation of anti-insulin antibodies that led to lipoatrophy and insulin resistance.

INSULIN

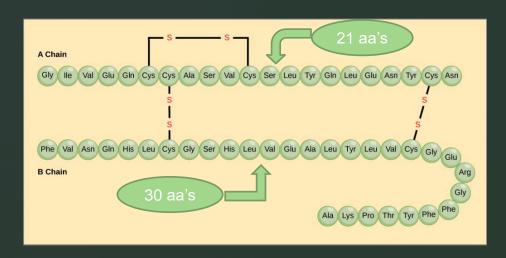
- A polypeptide hormone produced by the β-cells of the Islets of Langerhans in the pancreas.
- It influences the metabolism of carbs, fat and proteins.
- It is an anabolic hormone.
- First hormone to be isolated, purified and synthesized.
- First hormone to be sequenced and produced by DNA recombinant technology.

EVOLUTION OF INSULIN



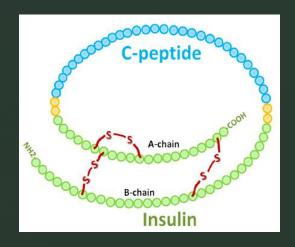
STRUCTURE OF INSULIN

INSULIN

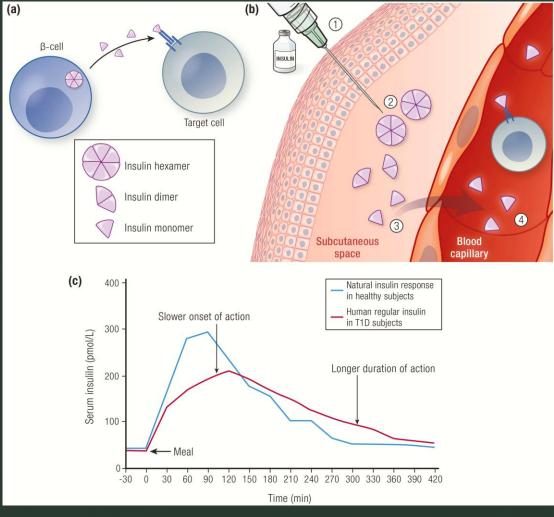


- A and B chains are linked by 2 disulfide bridges.
- The A chain has an intrachain disulfide bridge.

PROINSULIN



 Comes from a proinsulin precursor after the proteolytic excision of the C-peptide, which has no biological activity but is used as a measure of endogeneous insulin secretion.



Diabetes Care 1995;18(11):1452-9

- Insulin is stored in β-cells as hexamers stabilized by zinc.
- When released or injected to the circulation, zinc is released and the hexamers disassemble into monomers that can bind to insulin receptors in target cells.

PHYSIOLOGY OF INSULIN

- Endogeneous insulin has a circulatory half-life of 3-5 mins.
- In normal persons, after ingestion of food, insulin peripheral concentration:
 - 1. Increases within 8-10 mins
 - 2. Peaks by 30-45 mins
 - 3. Rapidly declines to baseline values by 90-120 mins postprandially

TODAY...

- There are 6 main types of insulin produced by the 3 insulin manufacturers serving the US market, each varying by onset, peak and duration of action:
 - short-acting or "regular" insulin
 - rapid-acting
 - intermediate-acting
 - long-acting
 - ultra-long acting
 - "premixed" insulin

What has improved in insulin therapy?

- Pharmacodynamics:
 - --faster insulins that better mimic our insulin production
 - --insulins that last longer and have no peaks
 - --minimal risk of nocturnal hypoglycemia
- Diabetes technology:
 - --better insulin pumps
 - --more accurate CGM's
 - --smart pens that record insulin dosing

ULTRA-RAPID INSULINS



- Fiasp (Novo's aspart)
- Can be dosed at first bite or within 20mins of starting a meal while Novolog is dosed 5-10mins before a meal.
- Its formulation contains the addition of vitamin B3 (niacinamide) that increases the speed of initial absorption and an amino acid L-arginine that stabilizes the formulation.
- Onset of action occurs 5 to 6 mins faster than insulin aspart.

FDA-approved for use in 2017, for use in pumps in 2019 and for use in children in 2020.

ULTRA-RAPID INSULINS

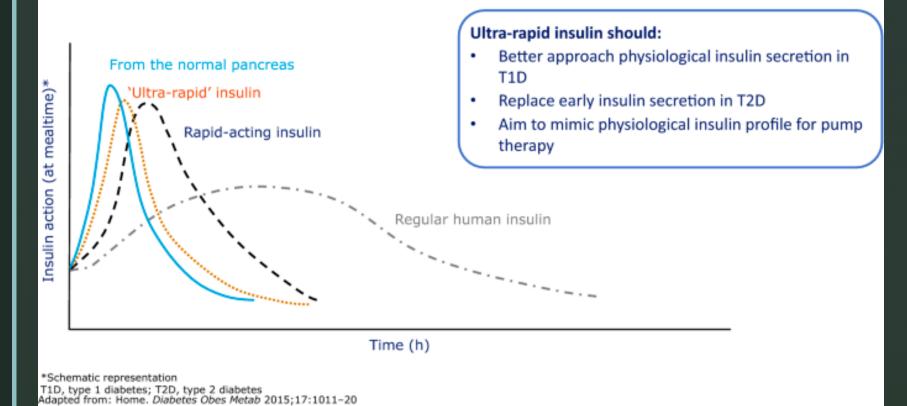


- Lyumjev (Lilly's lispro)-approved in June 2020
- Utilizes two locally acting excipients: citrate increases vascular permeability at the site of injection whereas treprostinil causes increased local vasodilation, with no measurable systemic exposure.
- Lyumjev begins working in the body within 13 minutes, compared to Humalog that can take as long as 27 minutes although trials show noninferiority in terms of A1c reduction.
- It can be taken at the start of a meal, or within 20 minutes of starting to eat.

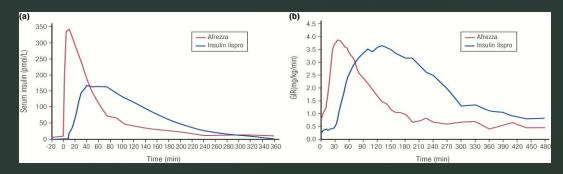
Appears to have more injection site reactions, burning and pain than other insulins.



Ultra-rapid insulin: approaching a physiological insulin profile even further



Still unable to mimic exactly the physiological insulin kinetics. The delay in onset still there since subcutaneous insulin needs to be absorbed from fatty tissue.



INHALED INSULIN

J Diabetes Sci Technol. 2017;11(1):148–156

- Afrezza (2014) is a recombinant human regular insulin that has been formulated as a dry powder to be inhaled by Technosphere technology.
- Approved nearly a decade after the first powdered native human insulin (Exubera, Pfizer) was withdrawn from the market in 2007 due to low sales (needs a lot of powder for small amount of insulin to reach the circulation).
- Afrezza starts working 12 to 15 mins after inhalation but a shorter duration of action compared to rapid and fast insulins.
- Contraindicated in asthmatics and smokers.
- Dosing is different from injectable insulin, so patients need some training.



INTERMEDIATE-ACTING INSULIN



- In 1936, when HC Hagedorn and B. Jensen found that the addition of protamine (a protein obtained from the semen of trout) could prolong the effects of injected insulin by precipitating the insulin hexamers.
- The most widely used were the protamine zinc insulin and lente insulins that are still used in veterinary practice.
- In 1950, neutral protamine hagedorn (NPH) insulin, or isophane insulin, became available as the first intermediate-acting insulin, with a slower onset and longer duration of action that allowed patients to sleep through the night!
- NPH insulin needs to be administered twice-daily to achieve adequate basal coverage.

NPH needs to be resuspended by rolling it gently 12-15 times prior to injection to avoid day-to-day variability.

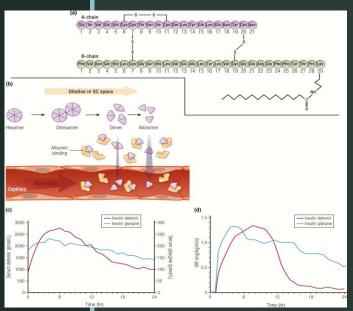
LONG-ACTING INSULIN ANALOGS



- So, the first long-acting insulin analog, insulin glargine, marketed as Lantus[®] (Sanofi), was first approved in the United States in the year 2000.
- In the s/q space, glargine undergoes pH-induced precipitation that dissolves slowly, providing a flattened peak and a median duration of action of up to 24 hours.

Remember: Insulin glargine should not be mixed with other forms of insulin due to the low pH of its diluent.

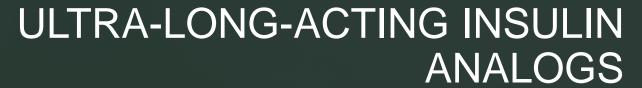
LONG-ACTING INSULIN ANALOGS



Diabetes Care. 2007; 30(10):2447–2452

- The second long-acting analog approved was detemir (Levemir-Novo) in 2005.
- Has a 14-carbon fatty acid side chain that stabilizes the hexamers to slow their dissociation and binds the detemir to albumin, both of which prolong the persistence of the insulin at the injection site.
- Compared to NPH, detemir has a slower onset, peaks at 6hrs and lasts up to 16hrs.
- Compared to glargine, detemir has a shorter duration and must be given twice daily.

Detemir requires larger doses but has less glycemic variability since it remains in solution form (does not precipitate).

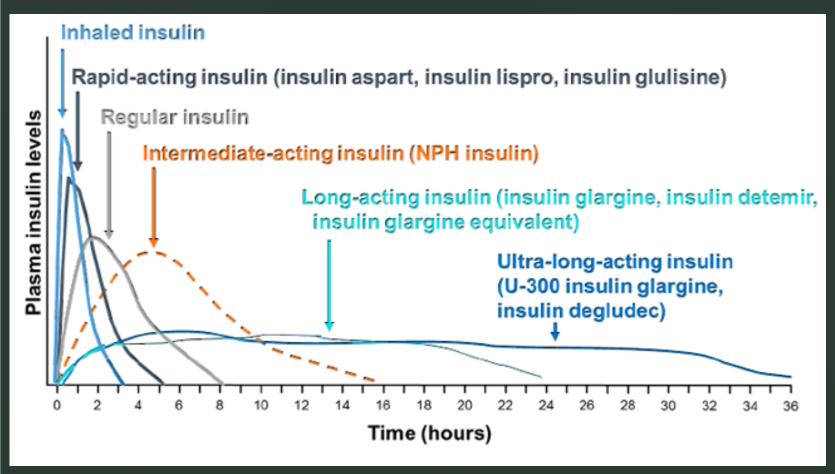




- Insulin degludec (*Tresiba*-Novo) approved by FDA in 2015 is the longest-acting insulin analog on the market today.
- Has a side chain with glutamic acid and a 16-carbon fatty acid that promote association into multihexamers complexes and also binds to albumin, both of which significantly slows dissociation and clearance.
- Degludec has a duration of action of at least 42hrs at steady state and can be given once daily at flexible dosing times.

Like detemir, requires higher doses than glargine for similar glycemic control due to albumin binding.

ADVANTAGES OF ULTRA-LONG-ACTING INSULINS



Overall, the predictable time-action profiles of long-acting insulin analogs, with flattened peaks and prolonged duration of action, do a better job of mimicking endogenous basal insulin secretion compared to intermediate-acting insulins, such as NPH.

These properties of the long-acting analogs may also reduce the risk of hypoglycemia, especially nocturnally.

**Keep in mind Tresiba's long duration when patient is put NPO for surgery, or is switched to another basal or to a pump.

PREMIXED INSULIN FORMULATIONS

- Human
 - Humulin 70/30
 - Novolin 70/30

- Human premixes must be injected
 30-45 mins before meals.
- Have a lower peak than Regular insulin but longer duration from the NPH component.

- Analogs
 - Humalog Mix 75/25 & 50/50
 - Novolog Mix 70/30
 - Ryzodeg 70/30

- Can be injected shortly before meals and 1 to 3 times daily.
- Humalog and Novolog Mix have a protamine suspension like NPH.
- Ryzodeg is the only analog-analog mix (aspart and degludec) and has longer duration than other mix

Insulin Mixes have the advantage of fewer injections compared to basal/bolus therapy.

Best suited for patients with consistent food intake and timing of their meals (since individual insulin components cannot be adjusted separately).

MIXING INSULINS

- NPH and Regular insulin when mixed in same syringe, can be used immediately or stored for future use.
- When rapid-acting analogs and NPH are mixed in same syringe, should be injected within 15 mins before a meal.
- When mixing Regular or rapid-acting insulins with NPH, the clear rapid- or short-acting insulin should be drawn into the syringe first.
- [Should avoid introducing NPH to R insulin since will change its pharmacokinetics]

INJECTION SITE CONSIDERATIONS

- The abdomen has the fastest rate of absorption, followed by the arms, thighs, and buttocks.
- Exercise increases the rate of absorption from injection sites, probably by increasing blood flow to the skin and perhaps also by local actions.
- Areas of lipohypertrophy usually show slower absorption.

CONCENTRATED INSULINS

- Bioequivalent to 100U/mL (no dose adjustment needed)
 - -- Insulin Lispro (200U/mL).
 - -- Insulin Degludec (200U/mL)

Same effectiveness but in half the volume.

- Not bioequivalent to 100U/mL (different time action profiles)
 - -- Insulin glargine (Toujeo-300U/mL)
 - -- Human Regular insulin (Humulin R U-500- 500U/mL)



CONCENTRATED INSULINS: TOUJEO

- A 3-fold concentrated version of insulin glargine was developed that showed less diurnal variation in glucose-lowering activity.
 - Insulin glargine U-300 (300 U/mL) was approved by the FDA in 2015 and marketed as Toujeo® (Sanofi).
- The higher concentration of glargine delivered in the same volume further slows the dissolution of the glargine precipitate in the SC space, leading to a lower peak and a longer duration of action compared to U-100 insulin glargine at the same U/kg dose.

Toujeo requires aprox. 15% more insulin for the same glycemic control (so reduce 20% if going back to U-100).

CONCENTRATED INSULINS: U-500 R



- With the epidemic of obesity and type 2 diabetes, the number of people requiring high doses of insulin has been growing.
- U-500 insulin beef regular was first available in 1952, and later U-500 insulin pork regular entered the market in 1980. These insulins were initially produced to overcome insulin resistance associated with high concentrations of anti-insulin antibodies from animal-sourced insulins.

With the advent of recombinant DNA technology, human regular *U-500* insulin, marketed as *Humulin® R U-500* (Lilly) was introduced in 1997 without the same immunogenic properties as its animal-sourced counterpart.

CONCENTRATED INSULINS: HUMULIN R U-500

- Indicated in severe insulin resistance, defined as an insulin requirement > 2U/kg/day or 200U a day.
- Such large volumes cause considerable discomfort at the injection site and problems with absorption.
- Given the similar onset and peak action to U-100R, the U-500R formulation provides prandial coverage while its extended duration of action provides basal insulin properties.
- Dosed 2-3 times daily with meals.

Humulin R U-500: New Devices (2016)

 Kwik Pen that holds 1,500U per pen and dosing in 5U increments.



Specific syringe for U-500.



These devices avoid the previous errors in administration and the need to convert doses when using U-100 syringe.

Biosimilars/Follow-on Biologics

Basaglar (Lilly 2015) – biosimilar to Lantus

Admelog (Sanofi 2017) - biosimilar to Humalog

Increase the number of treatment options available to patients and may increase accessibility of treatments and potentially reduce costs.



HYBRID-CLOSED LOOP SYSTEMS

Minimed 670G System (2017- from 14 y/o).

(2018- expanded approval from 7 y/o)

 SmartGuard technology with automated adjustments to the basal insulin infusion rates based on CGM readings and Suspend before Low.



T:slim X₂ with Control IQ algorithm (2019)

 In addition to above, has automated bolus corrections based on CGM and no calibration if used with DexcomG6.

Minimed 770G System (Sept 2020)

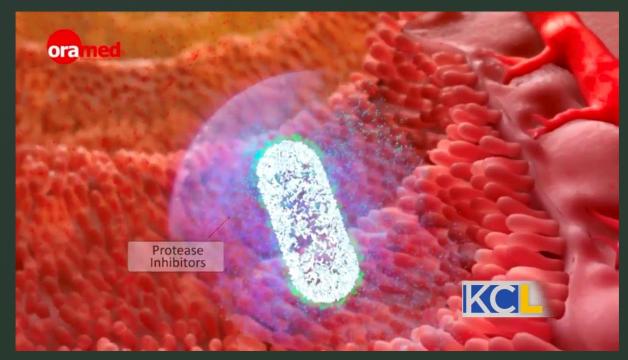


 An upgraded Bluetooth-enabled version of 670G providing smartphone connectivity to user and caregiver, and expanded indication from 2 years of age.

COMING ATTRACTION FOR INSULIN

ORAL INSULIN

- An oral (capsule) insulin formulation is in phase 2b trial by Oramed Pharmaceuticals, pending FDA approval for a phase 3 trial.
- Passes the intestinal wall intact and into the liver where it exerts its action.



It's been studied for NASH.

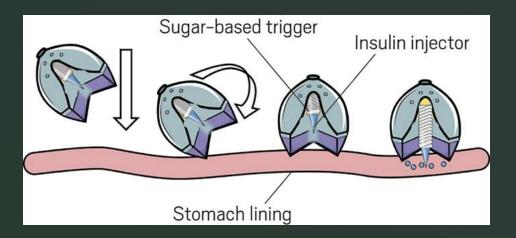


Oral-lyn from Generex

- A buccal insulin spray for prandial control, is still been improved and reformulated since 2015.
- Patients refer it has an odd taste and concerns on its effect on buccal mucosa.
- Requires too many sprays for a single dose of insulin.
- Does not enter the lungs so there are no pulmonary concerns.
- Was removed from India in 2009 when it was discovered had not been tested in humans.

SOMA Device



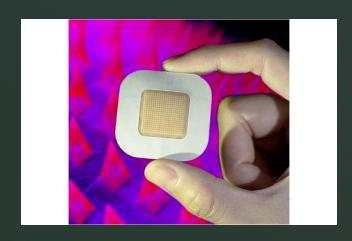


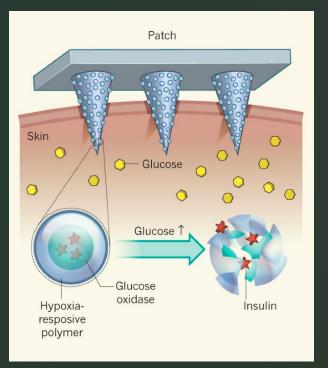
- NIH developed an ingestible applicator that engages with GI tissue and injects insulin through a self-orienting, millimeterscale applicator or SOMA device. (2019)
- The injector has compressed freeze-dried insulin.

SMART PATCH

- A quart-sized "smart" transdermal patch in animal trials, bearing microneedles loaded with insulin and a glucose-sensing polymeric matrix that swells when unites with glucose, causing insulin release.
- Intended for once-a-day use.
- It releases insulin in parallel with fluctuations of glucose.

[application for FDA approval to conduct trials in humans is underway]





INSULIN ICODEC

- A novel, super-long-acting basal insulin- dosed as a once-weekly injection.
- Has a time to maximum concentration of 16 hours and half-life of approximately 1 week.
- It is a native insulin molecule genetically fused to an elastin-like polypeptide biopolymer that releases insulin slowly.
- In clinical trials weekly icodec has resulted in similar glycemic control to daily glargine, similar rates of hypoglycemia and better post-breakfast and post-lunch glucose.
- A coformulation with a weekly GLP-1 is entertained. [concerns with titration]

Comparing Insulin Prices in the United States to Other Countries: Results from a Price Index Analysis by the U.S. Department of Health and Human Services

- Insulin prices are more than eight times higher in the United
 States than in 32 high-income comparison nations combined
- U.S. prices were higher than each of the 32 comparison countries individually, ranging from 3.8 times higher than those in Chile to 27.7 times those in Turkey. U.S. prices were 6.3 times higher than those in Canada, 5.9 times higher than those in Japan, and 8.9 times higher than those in the United Kingdom.
- Even with rebates and discounts (that may drive down prices by as much as 50%), the prices paid by U.S. consumers are likely to be 4X the average paid in other high-income nations.

It is estimated that 25% of patients stop or significantly reduce their insulin due to high costs.

SUMMARY

- Replacement insulin therapy should mimic the body's own insulin response as closely as possible.
- Despite vast improvements in the chemistry of insulin molecules to make them more physiological, exogenous insulin therapy still requires dose calculations and glucose monitoring.
- Advances in insulin's molecular properties through new analogs, coupled with advances in glucose monitoring and dosing algorithms, will continue to make insulin therapy safer and more effective for people with diabetes.

