New treatments for an old disease
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Associate Professor of Medicine
IU School of Medicine

Type 2 Diabetes Mellitus
that is hitting back
with
vengeance
USA.

A new Diabetic case Dx every 20 secs (1.7 million/yr)

Diabetes kills 1 American every 3 minutes

180 diabetics loose a limb every 24 hrs

55 Diabetics end on dialysis every 24 hrs
Globally, same mess, only Bigger!
Estimated global prevalence of diabetes

- **NA**
  - 2000: 19.7
  - 2011: 33.9
  - 2040: 72%

- **EU**
  - 2000: 17.8
  - 2011: 25.1
  - 2040: 41%

- **LAC**
  - 2000: 13.3
  - 2011: 33.0
  - 2040: 248%

- **SSA**
  - 2000: 7.1
  - 2011: 18.6
  - 2040: 261%

- **MEC**
  - 2000: 20.1
  - 2011: 52.8
  - 2040: 263%

- **China**
  - 2000: 20.8
  - 2011: 42.3
  - 2040: 204%

- **India**
  - 2000: 31.7
  - 2011: 79.4
  - 2040: 251%

- **A+NZ**
  - 2000: 1.2
  - 2011: 2.0
  - 2040: 65%

Diabetes doesn’t develop overnight; it takes years of preparation.
More **Insulin** to suppress lipolysis

- Liver
- Visceral Adiposity
- Cardiac Muscle
- Skeletal muscle

**Feeding**
β-Cell mass in Type 2 diabetes

ND=non-diabetic; IFG=impaired fasting glucose; T2DM=Type 2 diabetes mellitus
Butler et al. *Diabetes*. 2003
Pathogenesis of Type 2 Diabetes

- HGP = hepatic glucose production.

- Islet β-cell

- Impaired Insulin Secretion

- Increased HGP

- Decreased Glucose Uptake

Insulin Secretion and Insulin Resistance in Different Ethnic Populations With IGT

Decrease in AIR Necessary to Convert From NGT to IGT

Insulin resistance:

- Pima Indian: -8
- Latino/Hispanic: -18
- White: -32

AIR=acute insulin response to glucose.

Hormones in Sequence

**insulin secretion**

AIR

**Beta Cells**

**Amylin**

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**GLP-1: Secreted upon the ingestion of food**

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**Without diabetes; n = 27**

Late-stage type 2; n = 12

Type 1; n = 190

The **Incretins** “Gut-derived factors that increase glucose-stimulated insulin secretion” (Intestine Secretion of Insulin)

- **Gut**: Gut-derived factors that increase glucose-stimulated insulin secretion
  - **GLP-1**: Secreted upon the ingestion of food
    - Promotes satiety and reduces appetite
  - **Beta cells**: Enhances glucose-dependent insulin secretion
  - **Liver**: Glucagon reduces hepatic glucose output
    - α cells: Postprandial glucagon secretion
  - **Stomach**: Helps regulate gastric emptying
    - Beta-cell workload

The Incretin Effect is Reduced in Subjects with Type 2 Diabetes

The Incretin Effect accounts for ~60% of total Insulin release following a meal.

Control subjects

Subjects with type 2 diabetes


*P ≤.05 compared with respective value after oral load.
GLP-1 Is Cleaved and Inactivated by DPP-4

\[ T_{1/2} = 1 \text{ to } 2 \text{ min} \]
Development of more incretin mimetics

Native human GLP-1

Liraglutide

liraglutide OD

$T^{1/2}$ 13 h

Exenatide

exenatide

$T^{1/2}$ 2.4 h

Liraglutide has 97 % AA sequence identity with human GLP-1

## Chemical Structures of GLP-1 RAs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial</th>
<th>Titrate</th>
<th>Max</th>
<th>Dose Adjustments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide IR (Byetta®)</td>
<td>5 mcg BID within 60 mins of a meal (&gt; 6H between doses)</td>
<td>↑ to 10 mcg after 1 month</td>
<td>10 mcg</td>
<td>Renal impairment: CrCl 30-50 mL/min: use caution; CrCl &lt; 30 mL/min not recommended</td>
</tr>
<tr>
<td>Exenatide ER (Bydureon®)</td>
<td>2 mg once weekly</td>
<td></td>
<td>2 mg once weekly</td>
<td>Hepatic impairment: not studied</td>
</tr>
<tr>
<td>Liraglutide (Victoza®)</td>
<td>0.6 mg once daily</td>
<td>1.2 mg once daily per week</td>
<td>1.8 mg once daily</td>
<td>Renal &amp; hepatic impairment: use caution – limited experience</td>
</tr>
<tr>
<td>Albiglutide (Tanzeum®)</td>
<td>30 mg once weekly</td>
<td>↑ to 50 mg once weekly if inadequate response</td>
<td>50 mg once daily</td>
<td>Renal impairment: use caution when initiating or escalating doses</td>
</tr>
<tr>
<td>Dulaglutide (Trulicity®)</td>
<td>0.75 mg once weekly</td>
<td>↑ to 1.5 mg once weekly if inadequate response</td>
<td>1.5 mg once weekly</td>
<td>Renal impairment: use caution when initiating or escalating doses</td>
</tr>
</tbody>
</table>

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**Note:**
- Renal impairment: use caution when initiating or escalating doses
- Hepatic impairment:
  - Dulaglutide: use caution when initiating or escalating doses
  - All others: not studied, unlikely required

**Drug Initial Titrate Max Dose Adjustments**

- Exenatide IR (Byetta®): 5 mcg BID within 60 mins of a meal (> 6H between doses) ↑ to 10 mcg after 1 month 10 mcg
- Exenatide ER (Bydureon®): 2 mg once weekly
- Liraglutide (Victoza®): 0.6 mg once daily 1.2 mg once daily per week 1.8 mg once daily
- Albiglutide (Tanzeum®): 30 mg once weekly ↑ to 50 mg once weekly if inadequate response 50 mg once daily
- Dulaglutide (Trulicity®): 0.75 mg once weekly ↑ to 1.5 mg once weekly if inadequate response 1.5 mg once weekly

**Dose Adjustments**
- Renal impairment: use caution when initiating or escalating doses
- Hepatic impairment:
  - Dulaglutide: use caution when initiating or escalating doses
  - All others: not studied, unlikely required

**Initial Titrate Max**
- Exenatide IR (Byetta®): 5 mcg BID within 60 mins of a meal (> 6H between doses) ↑ to 10 mcg after 1 month 10 mcg
- Exenatide ER (Bydureon®): 2 mg once weekly
- Liraglutide (Victoza®): 0.6 mg once daily 1.2 mg once daily per week 1.8 mg once daily
- Albiglutide (Tanzeum®): 30 mg once weekly ↑ to 50 mg once weekly if inadequate response 50 mg once daily
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**Renal & hepatic impairment:**
- Exenatide IR (Byetta®): use caution when initiating or escalating doses
- Exenatide ER (Bydureon®): use caution when initiating or escalating doses
- Liraglutide (Victoza®): use caution – limited experience
- Albiglutide (Tanzeum®): use caution when initiating or escalating doses
- Dulaglutide (Trulicity®): use caution when initiating or escalating doses

**Hepatic impairment:**
- Exenatide IR (Byetta®): not studied, unlikely required
- Exenatide ER (Bydureon®): not studied
- Liraglutide (Victoza®): not studied
- Albiglutide (Tanzeum®): not studied
- Dulaglutide (Trulicity®): use with caution
Deciding about First Injectable Drug for Patients Not Controlled by Oral Agents

- **DURATION-3** trial of once-weekly exenatide vs insulin glargine as first injectable therapy

<table>
<thead>
<tr>
<th>3-year endpoint</th>
<th>Exenatide QW (n=233)</th>
<th>Insulin glargine (n=223)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in A1C</td>
<td>-1.01%</td>
<td>-0.81%</td>
<td>0.03</td>
</tr>
<tr>
<td>Change in body weight</td>
<td>-5.5 lbs</td>
<td>+4.4 lbs</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypoglycemia (exposure-adjusted events)</td>
<td>0.3 events per patient-year</td>
<td>0.9 events per patient-year</td>
<td>NR</td>
</tr>
</tbody>
</table>

NR = not reported.
ITKA 650 osmotic pump for continuous Exenatide infusion implanted yearly

60 Mcg daily was found to be the most tolerable dose. Diab Care. Vol 36:2013, lancet 04/2016
Exenetide QMS once-monthly suspension dosing (Phase II study data)

- **Microsphere technology provides a continuous level of exenatide**: Microspheres consist of a biodegradable polymer that dissipates into CO₂ and water. Using a non-aqueous suspending medium of Medium Chain Trigs Miglyol 812 that keeps the microspheres suspended & preserved eliminating the need for reconstitution immediately before injection. (5, 8, 11 MG dosing) with efficacy & tolerability c/w Exenetide QW

Subcutaneous injection of microsphere suspension of exenatide

Individual microspheres aggregate and initial release of exenatide

Microsphere degradation and continued release of exenatide

Further degradation and metabolism of microsphere polymer provide sustained level of exenatide

DPP-4 Inhibitors Prevent the Inactivation of GLP-1

GLP-1
GLP-1 Receptor
GLP-1

Insulin release

DPP-4
DPP-4 Inhibitor

GLP-1 Receptor
GLP-1 Receptor

β cell

Insulin
GLP-1 Modulates Numerous Functions in Humans

GLP-1 Receptor Agonism

- Decreases food intake
- Slows gastric Emptying
- Improves first-phase insulin response

DPP-4 Inhibition

- Suppresses glucagon secretion, decreasing glucose output
- Stimulates glucose-dependent insulin secretion

### Comparison of Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Sitagliptin (Januvia)</th>
<th>Linagliptin (Tradjenta)</th>
<th>Saxagliptin (Onglyza)</th>
<th>Alogliptin (Nesina)</th>
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</thead>
<tbody>
<tr>
<td><strong>Dose frequency</strong></td>
<td>100 mg QD</td>
<td>5 mg QD</td>
<td>5 mg QD</td>
<td>6.25mg, 12.5,25 QD</td>
</tr>
<tr>
<td><strong>Half-life (t_{1/2}), h</strong></td>
<td>12.4</td>
<td>12.5-21.1</td>
<td>2.2-3.8</td>
<td>21 hrs</td>
</tr>
<tr>
<td><strong>DPP-4 inhibition at 24 h</strong></td>
<td>~80%</td>
<td>~80% (25 mg)</td>
<td>~55% (5 mg)</td>
<td></td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td>Kidney (mostly unchanged)</td>
<td>Not kidney (unchanged)</td>
<td>Liver and kidney Active metabolite</td>
<td></td>
</tr>
<tr>
<td><strong>Renal dose adjustments required</strong></td>
<td>Yes</td>
<td></td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Selectivity for DPP-4</strong></td>
<td>&gt;2600-fold vs DPP-8 &gt;10,000-fold vs DPP-9</td>
<td>&gt;10,000-fold vs DPP-8/9</td>
<td>&gt;400-fold vs DPP-8 &gt;100-fold vs DPP-9</td>
<td></td>
</tr>
<tr>
<td><strong>Potential for drug–drug interaction</strong></td>
<td>Low</td>
<td>Low</td>
<td>Strong CYP3A4/5 inhibitors</td>
<td>No</td>
</tr>
<tr>
<td><strong>Food effect</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
The Kidneys Play an Important Role in the Handling of Glucose

- Total glucose stored in body: ~450 g
- Glucose utilization: ~250 g/day
  - Brain: ~125 g/day
  - Rest of body: ~125 g/day
- Glucose in Western diet: ~180 g/day
- Renal glucose production (gluconeogenesis + glycogenolysis): ~70 g/day
- Renal glucose filtration & reabsorption: ~180 g/day

Urinary glucose: 0 g

SGLT2 receptors
High Capacity/Low affinity @ Proximal Renal Tubules
Renal glucose re-absorption in healthy individuals

Filtered glucose load 180 g/day

SGLT2

~ 90%

SGLT1

~ 10%

Renal glucose re-absorption in patients with hyperglycaemia

When blood glucose increases above the renal threshold (~10 mmol/l or 180 mg/dL), the capacity of the transporters is exceeded, resulting in urinary glucose excretion.

Filtered glucose load > 180 g/day

SGLT2

~ 90%

SGLT1

~ 10%
Urinary glucose excretion via SGLT2 inhibition

Filtered glucose load $> 180$ g/day

SGLT2 inhibitors reduce glucose re-absorption in the proximal tubule, leading to urinary glucose excretion* and osmotic diuresis

*SGLT2 inhibitors reduce glucose re-absorption in the proximal tubule, leading to urinary glucose excretion and osmotic diuresis.

*Loss of $\sim 80$ g of glucose/day ($\sim 240$ cal/day).

## Renal Glucose Handling After SGLT2 Inhibition

<table>
<thead>
<tr>
<th></th>
<th>(CANAGLIFLOZIN)</th>
<th>(DAPAGLIFLOZIN)</th>
<th>(EMPAGLIFLOZIN)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosing Frequency</strong></td>
<td>QD</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dosage</strong></td>
<td>100 &amp; 300 mg</td>
<td>5 &amp; 10 mg</td>
<td></td>
</tr>
<tr>
<td><strong>Half-life (hours)</strong></td>
<td>10.6 – 13.1</td>
<td>~ 12.9</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>UGT1A9, UGT2BA</td>
<td>UGT1A9</td>
<td>UGT2B7, UGT1A3, UGT1A8, UGT1A9</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td>Fecal / Renal</td>
<td>Renal / Fecal</td>
<td>Renal / Fecal</td>
</tr>
<tr>
<td><strong>Renal Dosing</strong></td>
<td>&lt; 45 mL/min</td>
<td>&lt; 60 mL/min</td>
<td>&lt; 45 mL/min</td>
</tr>
<tr>
<td><strong>(eGFR): Not Recommended</strong></td>
<td>&lt; 45 mL/min</td>
<td>&lt; 60 mL/min</td>
<td>&lt; 45 mL/min</td>
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</table>

**References:**
## Large CV Outcomes Trials in Diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>SAVOR</th>
<th>EXAMINE</th>
<th>TECOS</th>
<th>CAROLINA</th>
<th>CARMELINA</th>
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<tbody>
<tr>
<td><strong>DPP4-i</strong></td>
<td>saxagliptin</td>
<td>alogliptin</td>
<td>sitagliptin</td>
<td>linagliptin</td>
<td>linagliptin</td>
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<tr>
<td>Comparator</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>sulfonylurea</td>
<td>placebo</td>
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<tr>
<td><strong>n</strong></td>
<td>16,500</td>
<td>5,400</td>
<td>14,000</td>
<td>6,000</td>
<td>8,300</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td>2013</td>
<td>2013</td>
<td>2015</td>
<td>2017</td>
<td>2017</td>
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<table>
<thead>
<tr>
<th>Study</th>
<th>LEADER</th>
<th>ELIXA</th>
<th>SUSTAIN 6</th>
<th>EXSCEL</th>
<th>REWIND</th>
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</thead>
<tbody>
<tr>
<td><strong>GLP1-RA</strong></td>
<td>liraglutide</td>
<td>lixisenatide</td>
<td><strong>semaglutide</strong></td>
<td>exenatide LR</td>
<td>dulaglutide</td>
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<tr>
<td>Comparator</td>
<td>placebo</td>
<td>placebo</td>
<td><strong>placebo</strong></td>
<td>placebo</td>
<td>placebo</td>
</tr>
<tr>
<td><strong>n</strong></td>
<td>16,500</td>
<td>14,000</td>
<td><strong>6,000</strong></td>
<td>5,400</td>
<td>8,300</td>
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<td><strong>Results</strong></td>
<td>6/2016</td>
<td>2015</td>
<td><strong>10/2016</strong></td>
<td>2018</td>
<td>2019</td>
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<th>CANVAS</th>
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<td><strong>SGLT-2-i</strong></td>
<td>empagliflozin</td>
<td>canagliflozin</td>
<td>dapagliflozin</td>
<td>ertugliflozin</td>
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<td>Comparator</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
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<tr>
<td><strong>n</strong></td>
<td>4300</td>
<td>22,200</td>
<td>3900</td>
<td>3900</td>
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<tr>
<td><strong>Results</strong></td>
<td>2017</td>
<td>2019</td>
<td>2020</td>
<td>EASD 2015</td>
</tr>
</tbody>
</table>
Number needed to treat (NNT) to prevent \textit{one death} across landmark trials in patients with high CV risk

- Simvastatin for 5.4 years
  - Pre-statin era
  - Pre-ACEi/ARB era
  - >75% statin

- Ramipril for 5 years

- Empagliflozin for 3 years
  - >80% ACEi/ARB

Insulin degludec from solution to subcutaneous depot

(Multi-hexamer formation key to protraction mechanism... Tresiba®)

As phenol from the vehicle diffuses degludec hexamers link up via single side-chain contacts

Long multi-hexamers assemble
Insulin degludec: slow release following injection

Subcutaneous depot

Zinc diffuses slowly causing individual hexamers to disassemble, releasing monomers

Monomers are absorbed from the depot into the circulation
**Insulin degludec: Mechanism of protraction**

Half-life is ~24 hours, duration >42 hours, steady state 2–3 days

Comes in 2 different degrees of green pens (Forest G/Garden G) U200 & U100
Timing of flexible insulin degludec administration

- 8-12 AND 36-40 hours between insulin administration
New Insulin Glargine 300 Units/mL Versus Glargine 100 Units/mL in People With Type 2 Diabetes Using Basal and Mealtime Insulin: Glucose Control and Hypoglycemia in a 6-Month Randomized Controlled Trial (EDITION 1)

For patients maintained on insulin glargine (U-100), expect a higher daily dose requirement of (U-300) to maintain the same level of glycemic control.

- Insulin detemir (Levemir®)
- Insulin glargine (Lantus®)
- Insulin glargine U300 (Toujeo®)
- Insulin glargine (Basaglar™)

<table>
<thead>
<tr>
<th>Insulin Type</th>
<th>Onset</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detemir</td>
<td>90 min</td>
<td>Up to 24 h</td>
</tr>
<tr>
<td>Glargine</td>
<td>90 min</td>
<td>Up to 24 h</td>
</tr>
<tr>
<td>Glargine U300</td>
<td>Up to 6 h</td>
<td>Up to 30 h</td>
</tr>
<tr>
<td>Glargine (Basaglar™)</td>
<td>Up to 24 h (glargine 24 h)</td>
<td>Up to 24 h (glargine 24 h)</td>
</tr>
</tbody>
</table>
Combination of Basal Insulin with a GLP-1 Agonist has a Scientific Logic

- **Insulin Degludec/Liraglutide** (Xultophy) P
- **Insulin Lantus/Lixisenitide** (iGlarlixi) OK

- **Modest weight** increase (1–3 kg)
  - Achieve A1C targets in ~50–60%

- **Weight lowering/neutral effects**
  - Achieve A1C targets in ~40–60%

**Additive effects**
Once-daily prandial lixisenatide versus once-daily rapid-acting insulin in patients with type 2 diabetes mellitus insufficiently controlled with basal insulin: analysis of data from five randomized, controlled trials.. GETGOAL DUO -2

% Patients achieving HbA1c <7%, no weight gain and no documented symptomatic hypoglycaemia

- Basal+LIXI: 29.2%
- Basal+RAI: 15.3%

P=0.0046

Triple Composite Outcome
Ultra rapid Acting Inhaled Insulin

- Pulling Zinc ions out will destabilize the hexamer structure allowing for quicker absorption.
- Max Blood concentrations within 15 mins, rapid hypoglycemic effect with 2-3 hrs total duration of action.
Technosphere® Insulin (AFREZZA™)

Technosphere insulin particles made up of diketopiperazine derivatives and insulin, which self-organize into a lattice array, and form particles of 2–4 µm diameter.

- **Peak Effect:**
  - SQ (RAA): ~1 hrs

- **Cough:** ~30%

- **No clinically meaningful changes in PFT’s (short-term)**
More Changes to Insulin Formulations

• **BioD-090(VIAject)** recombinant insulin + (EDTA); loosely packed insulin multimers with rapid dissociation into monomers & dimers.

• **Ultra-fast-acting insulin aspart (FIAsp)** recombinant insulin + nicotinamide & arginine causing increased local blood flow & so accelerated pharmacokinetics.

• **Hyaluronidase + analogue insulin** (uPH20/Hylenex) accelerated insulin action, time to peak, PP glycemic excursions reduced by 82 %, and statistically significant reduction in hypoglycemic events.

• **Injectable nano-network** (smart insulin); where Dextran nanoparticles loaded with insulin & glucose-specific enzymes, causing glucose-dependent insulin release
Hyaluronidases increase the dispersion of SC Insulin

Produces earlier and greater peak insulin concentrations, leading to improved postprandial glycemic control
Using Nanotechnology; Oral Insulin Delivery by PH Sensitive Microspheres

Gel/Microsphere system with polymethacrylic acid + PEG
In stomach (pH 2) pores in the polymer shrink & block protein release
In neutral pH (small intestine) the pores swell & release protein
The insulin canister hold 400 units and delivers 10 units per puff in a precisely metered dose. The formulated insulin is called Oral-lyn, had a 10% absorption. University of Toronto Researchers enhanced the Oral-lyn formulation, a 9-fold increase in serum insulin at 15 minutes and nearly 500 percent higher absorption of insulin over the 2-hour test period was verified in comparison to dogs that received the original formulation; a 33 percent decrease in serum glucose around minute 30 for the enhanced Generex Oral-lyn noted in comparison to a 12 percent increase in serum glucose in those that received the original formulation.

It may be taken just before the first bite and just after the last. This flexibility offers both Type 1 and Type 2 patients a unique opportunity to aggressively treat diabetes with a minimal risk of hypoglycemia.

The formulated insulin is stable at room temperature (North America) for 6 months or more. The micelles that are formed, containing the insulin, are > 7 microns and cannot enter the deep lungs regardless of effort. It is important to remember that only 20±40% of subcutaneous injection is absorbed. As will be mentioned below, insulin appears in the blood within 5 min, peaks at 30 min and is back to baseline at 24 hr «7KLV narrow window is unique to buccal insulin. It is possible because of the rich vascularity below the buccal epithelium. As with nitroglycerin, the insulin PK-PD is very fast, thus affording flexibility. The lack of a ‘tail' of insulin activity would favor less hypoglycemia.
Older Therapies revisited
( teaching old dogs new tricks)

<table>
<thead>
<tr>
<th>Formulations</th>
<th>ORAL METFORMIN</th>
<th>Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate release</td>
<td>IR</td>
<td>Rapid gut absorption</td>
</tr>
<tr>
<td>Extended release</td>
<td>XR</td>
<td>Prolonged gut absorption</td>
</tr>
<tr>
<td>Delayed release</td>
<td>DR</td>
<td>Late gut absorption (ileum)</td>
</tr>
</tbody>
</table>

BID or TID daily administration
GI side effects
Once daily administration
Less GI side effects
Once daily administration
Less GI side effects (?)
Enhanced GLP-1 secretion
Similar efficacy with lower dose
Less systemic exposure
Better safety if renal failure

DOI: 10.1517/14656566.2016.1149166
Copyright © 2016 Informa UK Limited, trading as Taylor & Francis Group
Effect of TZD (Pioglitazone) & on Fat Topography
Recent Data from IRIS trial

(Insulin Resistance Intervention after Stroke)

(Pio reduced DM risk by 52% in Stroke Pts, Reduced MACE by 24% over 5 yrs)

DeFronzo RA, JCEM 89:463-478, 2004
Any questions?