“New horizons for Therapy in Type 2 Diabetes”
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Pediatric Endocrinology

Obesity Facts

• During the past 20 years, there has been a dramatic increase in obesity in the United States.
• More than one-third of U.S. adults (35.7%) and approximately 17% (12.5 million) of children and adolescents aged 2—19 years are obese.
• 1 of 7 low-income, preschool-aged children is obese.

2011 National Diabetes Fact Sheet

• Diabetes affects 25.8 million people, 8.3% of the US population
  – Diagnosed: 18.8 million
  – Undiagnosed: 7 million
• In people younger than 20 yrs about 215,000 had diabetes (T1DM & T2DM) in the United States in 2010
Type 2 Diabetes Mellitus (T2DM)

- Fasting BS ≥ 126 mg/dL (≥ 7.0 mmol/L)
- 2hr OGTT- two hours after the oral glucose dose a plasma glucose ≥ 200 mg/dL (11.1 mmol/L)
- HgbA1C ≥ 6.5% diagnostic
- Symptomatic with a random blood sugar ≥ 200 mg/dL (≥ 11.1 mmol/L)

Ominous Octet

Metformin... multiple years of medical experience

- Biguanide Class
- Liver- main effect is a reduction in hepatic glucose output, largely due to a reduction in the rate of gluconeogenesis and a small effect upon glycogenolysis
- Decreases insulin resistance mainly in liver and muscle and to a lesser extent in adipose tissue

Metformin

- Benefits:
  - Weight neutral/mild weight loss
  - Modest improvement in LDL and TG
  - Thought to have an antioxidant effect
- Contraindications:
  - Renal Impairment (Creatinine >1.7 mg/dL)
  - Liver Disease (Transaminases >2.5x above normal)
  - Lung Disease that leads to acute/chronic hypoxia
  - DKA/Lactic acidosis.
Metformin

- Usual dosing in children >10 yrs
  - Metformin 500 mg po BID
- Usual dosing in Adolescents
  - Metformin 1000 mg po BID

Insulin... what lies in the future?

- In 1921 Frederick Banting and Charles Best successfully isolate insulin
- Long Acting Insulin
  - glargine (Lantus®):
    - Long-acting basal insulin analogue given once daily.
    - Microcrystals in an acidic pH that slowly release insulin.
    - Duration of action of 18 to 26 hours, with a "peakless" profile.
    - May provide up to ½ total daily insulin dose
    - May be given in combination with metformin or exenatide

Insulin

- detemir (Levemir®):
  - Long-acting basal insulin analogue given once daily.
  - Insulin analogue in which a fatty acid (myristic acid) is bound to the lysine amino acid at position B29.
  - Once injected SQ it is quickly absorbed binding to albumin in the blood through its fatty acid at position B29, then it slowly dissociates from this complex
  - Provides approximately 24hrs of coverage

Insulin

- degludec (Tresiba®):
  - Ultralong-acting basal insulin analogue that is active at physiologic pH.
  - Given SQ three-times a week with a duration of action that lasts up to 40 hours
  - Modified insulin that has one single amino acid deleted in comparison to human insulin, and is conjugated to hexadecanediolic acid via gamma-L-glutamyl spacer at the amino acid lysine at position B29
  - The addition of hexadecanediolic acid to lysine at the B29 position allows for the formation of multi-hexamers in subcutaneous tissues forming a subcutaneous depot that results in slow insulin release into the systemic circulation.

DPP-4 Inhibitors

- Dipeptidyl-peptidase IV (DPP-4) inhibitors inhibit the degradation of the incretins, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP)
- Berberine a common herbal dietary supplement inhibits dipeptidyl peptidase-4
DPP-4 Inhibitors

- Benefits:
  - ↓ HgbA1C by 0.5 to 1% similar to the reduction obtained with metformin and thiazolidinediones
  - Weight neutral
  - Slight improvement in HTN
  - Reduced doses can be used in those with renal impairment

- Adverse Effects:
  - Pancreatitis
  - Allergic Skin Reactions
  - Lymphopenia/Immune Suppression

Thiazolidinediones (TZD)

- The peroxisome proliferator-activated receptors (PPARs) are lipid-activated transcription factors that regulate the expression of genes that control lipid and glucose metabolism

- TZD:
  - Selectively stimulates the nuclear receptor PPAR-γ
  - Modulates the transcription of the insulin-sensitive genes involved in the control of glucose and lipid metabolism in the muscle, adipose tissue, and the liver
  - PPAR-γ plays a role in adipocyte differentiation
  - Inhibits VEGF-induced angiogenesis
  - ↓ Leptin (leading to ↑ appetite)
  - ↓ Certain interleukins (e.g. IL-6)
  - ↑ Adiponectin levels

Thiazolidinediones (TZD)

- ↓ Insulin resistance in the liver and peripheral tissues
- ↑ Expense of insulin-dependent glucose
- ↓ Withdrawal of glucose from the liver hence reduces quantity of glucose, insulin and glycated Hgb in the bloodstream.
- ↓ Triglycerides and ↑ HDL without changing LDL and total cholesterol in patients with disorders of lipid metabolism.
Thiazolidinediones (TZD)

- Side Effects:
  - Weight Gain
  - Fluid Retention/edema
- Contraindications:
  - Liver Disease
  - Congestive Heart Failure
- Concerns:
  - Increased Risk of Bladder Cancer
  - Increased Risk of Cardiovascular Events
- Drugs:
  - Rosiglitazone (Avandia®)
  - Pioglitazone (Actos®)

Sodium-dependent Glucose co-transporters (SGLT-2)

- Expressed in the S1 and S2 segments of the proximal convoluted tubule
- The glomeruli filter about 144 g of glucose per 24 h, nearly 100% of which is reabsorbed in the renal tubules.
- In normal non-diabetic kidneys glucosuria develops at BS 180mg/dL
- Diabetics up-regulate SGLT-2 to reabsorb more glucose.

Table 1: Type of Sodium glucose transporters

| Gene   | Protein Name | Organ | Type of Glucose Transport
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<tbody>
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<td>SLC5A1</td>
<td>glucose 1</td>
<td>small bowel, liver, kidney</td>
<td>xglycerol, xgalactose, xfructose, xglutamine</td>
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<tr>
<td>SLC5A6</td>
<td>glucose 2</td>
<td>kidney</td>
<td>xgalactose, xfructose, xgalactoside</td>
</tr>
<tr>
<td>SLC5A7</td>
<td>glucose 5</td>
<td>liver</td>
<td>xglycerol, xgalactose, xfructose, xfructose-1-phosphate</td>
</tr>
<tr>
<td>SLC5A8</td>
<td>glucose 6</td>
<td>liver</td>
<td>xgalactose, xfructose, xgalactoside</td>
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Table 2: Type of Sodium glucose transporter

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SGLT-2 Inhibitors

- Inhibit Reabsorption of 30-50% of filtered glucose load
- Improve hyperglycemia and cause weight loss (2.5 to 3.4 Kg) by inducing controlled glucosuria (loosing 200-300Kcal/day)

Benefits:
- Low risk of hypoglycemia
- Weight loss
- Improved BP
- Decrease glucotoxicity and indirectly helps β-cells
- Because of their unique mechanism of action, which is independent of the severity of insulin resistance and β-cell failure, type 2 diabetic individuals with recent-onset diabetes (<1 year) respond equally well as type 2 diabetic patients with longstanding diabetes (>10 years)
- Side effects - Some increase in genital infections at higher doses
- Drugs:
  - dapagliflozin (Forxiga® - approved in European Union Nov 2012)
  - Sergliflozin

GLP-1 Agonist

- Benefits:
  - ↓ HbA1c by 1.6% to 0.9%
  - Weight loss via delayed gastric emptying and ↓ appetite
- Side effects:
  - Nausea/Vomiting/Diarrhea
  - Dizziness
  - Headache
  - Jitteriness

Concerns:
- Acute Pancreatitis
- ↑ Risk of Thyroid Cancer and Pancreatic Cancer

Contraindications:
- Renal impairment
- Gastroparesis
- Hx of Thyroid Cancer

Ma, J. et al. Best Practice & Research Clinical Endocrinology & Metabolism 23 (2009) 413–424

Drucker, D and Nauck, M. Lancet 2006; 368: 1696–705
GLP-1 Agonist

- Therapy:
  - Maybe used in combination with metformin or with TZD.
  - Can also be combined with sulfonylureas

- Drugs:
  - Twice daily injection of exenatide (Byetta®)
  - Long-acting once a week injection of exenatide (Bydureon®)
  - Liraglutide (Victoza®)

Chronic exenatide infusion increases insulin sensitivity, decreases insulin secretion and stimulates islet cell proliferation in partially pancreatectomized baboons.

Continuous Exenatide Infusion

OBJECTIVE: Assess the effect of a continuous exenatide infusion after partial pancreatectomy, on in-vivo glucose metabolism, α-β-δ cell mass and islet function in baboons.

- Why Baboons?
  - Current imaging technology cannot accurately provide adequate pancreatic islet imaging.
  - Serial Biopsies in Humans would be unethical
  - Baboons share >95% genetic similarities with humans
  - Baboons are an excellent surrogate non-human primate model for the study of insulin resistance and T2DM.

SW Baboon Colony

N=24

2 Step Hyperglycemic Clamp

1st step: raise blood glucose +125mg/dL above fasting glucose
2nd step: +225 mg/dL above fasting glucose followed by an Arginine bolus (0.5g/kg)

Partial Pancreatectomy T (70% of pancreas excised)

Post-op recovery

Normal Saline Infusion N=12

33 μL Continuous Infusion

Exenatide (0.014μg/kg/h) N=12

72 hr Washout Period

Repeat 2 step Hyperglycemic Clamp

Euthanasia & Necropsy

Tissue Collection (head-body Pancreas ~70%)
Fig. 1 Islet mass differences between exenatide and saline groups. There is no significant difference in islet mass ($p=0.58$) between the pancreas tail vs. head-body in the exenatide group demonstrating increased islet mass in exenatide treated pancreas head-body when compared to saline.

Proliferation and apoptosis were expressed as % of cells counted.

**Panel A** – MIB1 staining, cell proliferation marker. EXE tail vs. head-body (0.07±0.03 vs. 0.43±0.06, $p=0.0001$). EXE vs SAL (0.43±0.06 vs 0.07±0.04, $p=0.0001$). **Panel B** – M30 staining, cell apoptosis marker. EXE tail vs head-body (1.58±0.58 vs 2.58±0.47, $p=\text{NS}$). SAL tail vs head-body (0.52±0.21 vs 1.75±0.55, $p=0.05$).

**Acknowledgements**

- **Dept. of Medicine, Diabetes Division** (UTHSCSA)
  - Franco Folli MD PhD – Professor of Medicine
  - Research Mentor
  - Francesca Casiraghi, MS
  - Subhash Kamath, MS
  - Andrea Ricotti, PharmD
  - Dr. Alberto Chavez-Velazquez
  - Dr. Rodolfo Guardado
  - Support: NIH, Amylin, Takeda

- **Dept. of Pediatrics, Endocrine and Diabetes Division**
  - Daniel Hale, MD
  - Jane Lynch, MD
  - W.M. Rogers, MD
  - Carisse Orsi, MD
  - Fellows and Nursing staff

- **Dept. of Pediatrics, Center at San Antonio, Texas**