LIRAGLUTIDE (IN ADDITION TO INSULIN) IN OVERWEIGHT PATIENTS WITH TYPE-1 DIABETES

BY NEHA LALANI MBBS

MENTORS: DR. NITESH KUHADIYA MD, MPH
DR. PARESH DANDONA MD, PHD
Background

Why is it difficult to control glycemic variations in type-1 diabetes?

- Autoimmune destruction of B-cells → near total loss of endogenous insulin production → cannot compensate for changing requirements (1)
- Insulin boluses → not precise doses or bioavailability (2)
- Lack of endogenous insulin → absence of post-prandial glucagon inhibition → hyperglucagonemia → glycemic variability and unpredictability not totally corrected with extrinsic insulin (3)
- Insulin (anabolic hormone) → 40-50% type-1 diabetic have metabolic syndrome → cardiovascular mortality (4)

What are GLP-1 agonists and how do they work?

- Glucagon like peptide-1 agonists
- Approved for treatment in type-2 diabetes
- Gut: Delay gastric emptying $\rightarrow$ ↓ appetite
- Pancreas: Stimulates insulin release when glucose is released from gut and inhibits glucagon release
- Liver: Reduces glucose production as glucagon secretion from pancreas is reduced

- Examples: Exenatide (BID and Q weekly) and Liraglutide (Q daily)
Previous studies with GLP-1 in type-1 diabetes

- Varanasi A et al: GLP-1 analogue in 13 patients with type 1 diabetes led to a remarkable reduction in the excursions of blood glucose, both highs and lows, following meals and through the 24 hours within the first 2 days of treatment in all 13 subjects.

- Kuhadiya et al: Retrospective study showed that addition of liraglutide to insulin in obese patients with type 1 diabetes mellitus leads to improvements in glycemic control and HbA1c and to reductions in insulin dose, systolic blood pressure, and body weight.

- Kielgast U et al: GLP-1 infusion suppresses basal and arginine induced glucagon secretion in subjects with type 1 diabetes.

- Rother Kl et al: GLP-1 infusion also completely prevents the rise in post-prandial glucose or glucagon concentrations in these patients.

- Ghanim H et al: (The importance of glucagon in inducing hyperglycemia is further strengthened by the observation that) glucagon receptor knockout mice do not develop diabetes inspite of complete B-cell destruction by streptozotocin.
Based on these studies it was clear that in addition to insulin replacement, glucagon suppression is an important part of treating type 1 diabetes.

We decided to further investigate the effect of liraglutide in type-1 diabetics.

This will be the first study to attempt to reduce body weight and other features of the metabolic syndrome, while improving glycemic control with addition of a single therapeutic agent in overweight and obese patients with type 1 diabetes.
Trial objectives and purpose

- Hypothesis 1: Treatment with Liraglutide in overweight or obese patients with type 1 diabetes decreases fasting, postprandial and the overall mean glucose concentrations while decreasing the dose of insulin required.

- Hypothesis 2: Treatment with liraglutide reduces abdominal adiposity, hepatic and visceral fat mass and improves features of metabolic syndrome.

- Hypothesis 3: Treatment with Liraglutide in obese patients with type 1 diabetes improves blood pressure.
Research design and methods

- Prospective, randomized, double blinded, placebo controlled study in overweight type-1 diabetics
- Setting: Diabetes-Endocrinology Center of WNY, affiliated to the State University of New York
- UB-IRB approved
**Inclusion criteria**

1) Type 1 Diabetes on continuous subcutaneous insulin infusion (CSII; also known as insulin pump) or multiple (four or more) injections of insulin per day

2) Using a continuous glucose monitoring device (CGM) or regularly measuring their blood sugars four times daily

3) HbA1c of less than 8.5%

4) Well versed with carbohydrate counting

5) Age 18-75 years

6) BMI $\geq 25$kg/m²

7) Age at diagnosis of type 1 diabetes should be $<30$ years.

8) evidence of auto-immunity to beta cells (GAD-65 and islet cell antibody screen)
Exclusion criteria

1) Type 1 diabetes for less than 6 months
2) Coronary event or procedure (myocardial infarction, unstable angina, coronary artery bypass, surgery or coronary angioplasty) in the previous four weeks
3) Hepatic disease (transaminase > 3 times normal) or cirrhosis
4) Renal impairment (serum eGFR < 30ml/min/1.73m²)
5) HIV or Hepatitis B or C positive status
6) Participation in any other concurrent clinical trial
7) Any other life-threatening, non-cardiac disease
8) Use of an investigational agent or therapeutic regimen within 30 days of study
9) History of pancreatitis
10) Pregnancy
Exclusion criteria contd...

11) Inability to give informed consent
12) History of gastroparesis
13) History of medullary thyroid carcinoma or MEN 2 syndrome
14) Smokers will be advised not to change their amount of smoking for the duration of the study
15) Use of any agent other than insulin for treatment of diabetes (metformin, pramlintide or thiazolidinediones)
16) Painful gallstones
17) Alcoholism
18) Hypertriglyceridemia (>500 mg/dl)
Study Description

- **Screening day**: History and physical, informed consent, baseline fasting CBC, CMP, lipid panel, c-peptide, GAD-65 antibody (with reflex to islet-cell antibody), HbA1c, fructosamine.

- **Day -14**: Visit with registered dietician (carbohydrate counting) and diabetic educator (injection technique); continuous glucose monitor for 2 weeks; baseline DEXA and MRI script given.

- **Day 0**: CGM data collected, 24 hour BP monitor given.

- **Day 1**: Study drug dispensed and started at 0.6mg sc QD;
  - If HbA1c < 7 – basal and prandial insulin dose reduced by 25%;
  - If HbA1c >7.5 – continue same insulin dose;
  - If HbA1c 7-7.5 – insulin dose reduced by 10%
Week 1 and week 2: Insulin pump download/ food logs reviewed; insulin adjustment made for target of pre-prandial 80-120 mg/dl, 2 hr post-prandial <140 mg/dl and avoid BG < 70; dose increased to 1.2 mg at week 1 and 1.8 mg at week 2 if tolerated.

Week 4 and 8: insulin dose adjusted and drug titrated up to maximum 1.8 mg

Week 12: Insulin dose adjusted; fasting blood collected for CBC, CMP, lipid profile, hemoglobin A1C and fructosamine; 24 hour BP monitor given.

Week 16 and 20: Insulin dose adjustment.

Week 24: insulin dose adjustment, DEXA MRI scripts given and CGM inserted

Week 26: CGM data collected, fasting blood sample collected and 24 hour BP monitor given.
Study discontinuation criteria

- Unable to tolerate drug because of severe nausea/vomiting
- Pancreatitis
- Thyroid tumour

Fortunately, we didn’t have any of the above.
### Primary end point
- Change in HbA1c

### Secondary end points
- Change in average daily glucose, average fasting glucose, glycemic variability (continuous glucose monitor data) and fructosamine
- Insulin doses
- Subcutaneous fat mass distribution (DEXA), hepatic fat fraction and visceral fat mass (MRI)
- 24 hour blood pressure

### Sample size
- So far 35 patients have completed the study: 18 in placebo group and 17 in drug group
- Randomization number was assigned using Microsoft Excel
Baseline Characteristics

No statistically significant difference in the following baseline characteristics:

- Age
- Mean age at Type-1 diabetes diagnosis
- Gender
- Weight/ BMI
- C-peptide antibody
- GAD-65 antibody positivity
- Body fat distribution
- Visceral adipose tissue
- Hepatic fat fraction
- Hemoglobin A1C
- Fructosamine
- Insulin dose (Total, basal and bolus)
- Carbohydrate intake and number of helpings
- Daily average glycemic variability
## Change in Weight, BMI, HbA1C and Fructosamine

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Change over 12 weeks</th>
<th>Change over 26 weeks</th>
<th>Change from 12 to 26 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Drug</td>
<td>P</td>
</tr>
<tr>
<td>Groups</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (lb)</td>
<td>-1.11±2.1</td>
<td>-9.35±1.5</td>
<td><strong>0.003</strong></td>
</tr>
<tr>
<td>BMI</td>
<td>-0.24±0.3</td>
<td>-1.48±0.3</td>
<td><strong>0.006</strong></td>
</tr>
<tr>
<td>Hemoglobin A1C (%)</td>
<td>+0.1±0.1</td>
<td>-0.38±0.1</td>
<td><strong>0.01</strong></td>
</tr>
<tr>
<td>(mmol/mol)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fructosamine (umol/L)</td>
<td>+14±9</td>
<td>+6.24±7</td>
<td>0.5</td>
</tr>
</tbody>
</table>

- **Weight and BMI**: Significant difference in weight reduction in placebo vs drug group in first 12 weeks, over 26 weeks. However, the effect seems to have stabilized between 12 to 26 weeks.

- **Hemoglobin A1C**: Increased in placebo group while decreased in drug group in first 12 weeks, statistically significant. Effect plateaued and no difference from 12 to 26 weeks and overall in 26 weeks.

- **Fructosamine**: No significant difference in change in fructosamine between two groups.
Change in Weight, BMI, HbA1C and Fructosamine
## Change in body fat distribution

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Change over 12 weeks</th>
<th>Change over 26 weeks</th>
<th>Change from 12 to 26 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo Drug p</td>
<td>Placebo Drug p p</td>
<td>Placebo Drug p p</td>
</tr>
<tr>
<td>Arm fat (g)</td>
<td>NA NA NA</td>
<td>-37±28 -231±146 0.32</td>
<td>NA NA NA NA</td>
</tr>
<tr>
<td>Leg fat (g)</td>
<td>NA NA NA</td>
<td>-91±206 -629±389 0.23</td>
<td>NA NA NA NA</td>
</tr>
<tr>
<td>Trunk fat (g)</td>
<td>NA NA NA</td>
<td>-9±534 -2371±748 0.014</td>
<td>NA NA NA NA</td>
</tr>
<tr>
<td>Total fat (g)</td>
<td>NA NA NA</td>
<td>-128±756 -3263±705 0.005</td>
<td>NA NA NA NA</td>
</tr>
<tr>
<td>Arm lean (g)</td>
<td>NA NA NA</td>
<td>+44±87 -28±104 0.59</td>
<td>NA NA NA NA</td>
</tr>
<tr>
<td>Leg lean (g)</td>
<td>NA NA NA</td>
<td>+6±206 -356±227 0.24</td>
<td>NA NA NA NA</td>
</tr>
<tr>
<td>Total lean (g)</td>
<td>NA NA NA</td>
<td>-13±455 -963±279 0.08</td>
<td>NA NA NA NA</td>
</tr>
<tr>
<td>Total BMC (g)</td>
<td>NA NA NA</td>
<td>+11±24 +61±117 0.67</td>
<td>NA NA NA NA</td>
</tr>
<tr>
<td>Total BMD (g/cm2)</td>
<td>NA NA NA</td>
<td>0±0 0±0 0.5</td>
<td>NA NA NA NA</td>
</tr>
<tr>
<td>Visceral adipose tissue (L)</td>
<td>NA NA NA</td>
<td>+0.15±0.26 -0.29±0.14 0.15</td>
<td>NA NA NA NA</td>
</tr>
<tr>
<td>Hepatic fat fraction (%)</td>
<td>NA NA NA</td>
<td>+0.54±0.17 +0.14±0.18 0.12</td>
<td>NA NA NA NA</td>
</tr>
</tbody>
</table>

- Significant difference between placebo and drug group in reduction in total fat and trunk fat over 26 weeks.
Change in body fat distribution
# Change in 24 hour blood pressure parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Change over 12 weeks</th>
<th>Change over 26 weeks</th>
<th>Change from 12 to 26 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Drug</td>
<td>p</td>
</tr>
<tr>
<td>24 hour mean SBP (mm Hg)</td>
<td>+9.8±3.4</td>
<td>-6.1±3.9</td>
<td><strong>0.01</strong></td>
</tr>
<tr>
<td>24 hour mean DBP (mm Hg)</td>
<td>+0.9±1.1</td>
<td>-0.7±1.4</td>
<td>0.43</td>
</tr>
<tr>
<td>24 hour mean pulse (mm Hg)</td>
<td>-0.8±2.9</td>
<td>+4±2.1</td>
<td>0.18</td>
</tr>
<tr>
<td>24 hour mean MAP (mm Hg)</td>
<td>+4.5±2.2</td>
<td>-2.3±2.3</td>
<td>0.06</td>
</tr>
<tr>
<td>24 hour SBP &gt; 140 (%)</td>
<td>+18.5±6.4</td>
<td>-6.02±7.41</td>
<td><strong>0.03</strong></td>
</tr>
<tr>
<td>24 hour DBP &gt; 90 (%)</td>
<td>+0.86±1.3</td>
<td>-3.17±2.45</td>
<td>0.16</td>
</tr>
</tbody>
</table>

- **24 hour mean SBP and % time > 140 mm Hg**: Increased in Placebo group and decreased in drug group over 12 and 26 weeks with statistically significant difference.

- **24 hour mean DBP and % time >90 mm Hg**: Decrease in drug group and increase in placebo group over 12 and 26 weeks, but not statistically significant difference.

- **Mean Arterial pressure**: Significant reduction in drug group over 26 weeks.
Change in 24 hour blood pressure parameters

24 Hr mean SBP (mm of Hg)

Mean Arterial Pressure (mm of Hg)

% time spent in SBP > 140 mm of Hg
## Change in insulin requirement

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Change over 12 weeks</th>
<th>Change over 26 weeks</th>
<th>Change from 12 to 26 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Drug</td>
<td>p</td>
</tr>
<tr>
<td><strong>Groups</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total insulin dose (units)</td>
<td>-7.27±4.6</td>
<td>-8.65±3.7</td>
<td>0.81</td>
</tr>
<tr>
<td>Total insulin dose (units/Kg)</td>
<td>-0.06±0.04</td>
<td>-0.06±0.04</td>
<td>0.9</td>
</tr>
<tr>
<td>Basal insulin dose (units)</td>
<td>-2.61±1.8</td>
<td>+3.6±2.29</td>
<td>0.74</td>
</tr>
<tr>
<td>Basal insulin dose (units/Kg)</td>
<td>-0.03±0.02</td>
<td>-0.02±0.02</td>
<td>0.9</td>
</tr>
<tr>
<td>Bolus insulin dose (units)</td>
<td>-5.44±3.53</td>
<td>-8.15±2.17</td>
<td>0.52</td>
</tr>
<tr>
<td>Bolus insulin dose (units/Kg)</td>
<td>-0.05±0.03</td>
<td>-0.07±0.02</td>
<td>0.5</td>
</tr>
</tbody>
</table>

- No significant difference in change in total, basal or bolus insulin dose requirement in drug or placebo groups.
### Change in carbohydrate intake and Glycemic indices

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Change over 12 weeks</th>
<th>Change over 26 weeks</th>
<th>Change from 12 to 26 weeks</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Groups</td>
<td>Placebo</td>
<td>Drug</td>
<td>Placebo</td>
<td>Drug</td>
</tr>
<tr>
<td>Average daily carbohydrate intake (g)</td>
<td>-15±19.7</td>
<td>+5.83±13.18</td>
<td>-9.38±14.54</td>
<td>+0.45±15.5</td>
</tr>
<tr>
<td>Average daily carbohydrate helpings (meals/day)</td>
<td>-0.01±0.18</td>
<td>-0.12±0.22</td>
<td>-0.448±0.3</td>
<td>-0.16±0.23</td>
</tr>
<tr>
<td>Average daily glucose (mg/dl)</td>
<td>NA</td>
<td>NA</td>
<td>+1±8</td>
<td>-4±9</td>
</tr>
<tr>
<td>Average fasting glucose (mg/dl)</td>
<td>NA</td>
<td>NA</td>
<td>+3±8</td>
<td>-15±13</td>
</tr>
<tr>
<td>% time spent &lt;55</td>
<td>NA</td>
<td>NA</td>
<td>+3±1</td>
<td>-1±1</td>
</tr>
<tr>
<td>% time spent 55-70</td>
<td>NA</td>
<td>NA</td>
<td>+5±2</td>
<td>-2±0</td>
</tr>
<tr>
<td>% time spent 70-160</td>
<td>NA</td>
<td>NA</td>
<td>-1±2</td>
<td>-1±3</td>
</tr>
<tr>
<td>% time spent 160-240</td>
<td>NA</td>
<td>NA</td>
<td>-6±3</td>
<td>-4±2</td>
</tr>
<tr>
<td>% time spent &gt;240</td>
<td>NA</td>
<td>NA</td>
<td>-1±2</td>
<td>0±4</td>
</tr>
</tbody>
</table>

**Carbohydrate intake and helpings**: Increased in drug group over 12 weeks and 26 weeks while decreased in placebo group, but not significant change.

**Glycemic Indices**: Decrease in average daily glucose, average fasting glucose and time spent in hypoglycemia in drug group while these parameters increased in placebo group. No significant difference in this change.
Conclusion

- Encouraging results with regard to HbA1c, weight/BMI, body fat distribution and blood pressure.
- We plan to recruit more patients in this study to increase the power.
- If this drug is shown to be consistently effective, it will provide a major advance in the treatment of hyperglycemia and unpredictable alterations in glucose concentrations in type 1 diabetes, a disease that is newly diagnosed in 15000 children per year in the US and currently affects 3 million Americans.
Acknowledgement

- Dr. Nitesh Kuhadiya
- Dr. Paresh Dandona
- Dr. Henri Woodman
Thank you!