LIRAGLUTIDE AS ADDITIONAL TREATMENT IN PATIENTS WITH TYPE 1 DIABETES MELLITUS

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OBJECTIVE

TO DETERMINE IF **ADDITION OF LIRAGLUTIDE** TO INSULIN IN T1D LEADS TO IMPROVEMENT IN GLYCEMIC CONTROL AND DIMINISHES GLYCEMIC VARIABILITY.
BACKGROUND

GLUCOSE HOMEOSTASIS IN TYPE 1 DIABETICS IS FRAGILE

- B-cell reserve is negligible.
- Cannot generate extra insulin to compensate for changing requirements.
- Extra insulin boluses may not match precise need in dose/bioavailability.
- Glucagon secretion by a-cell probably not suppressed in T1D.
- Erratic BG pattern may be due to hyperglucagonemia.
GLP-1 AGONISTS

- Glucagon like peptide agonists - class of drugs for type 2 diabetes.
- GLP-1 enhances glucose-dependent insulin secretion after release from gut.
- Exenatide & Liraglutide are add-on drug for T2D in whom hypoglycemia is of concern.
GLP-1 mediates various physiological effects on different organs:

- **Heart**: Cardioprotection and maintenance of cardiac output.
- **Brain**: Neuroprotection and regulation of appetite.
- **GI tract**: Regulation of gastric emptying and glucose production.
- **Liver**: Increased insulin sensitivity and glucose metabolism.
- **Muscle**: Increased insulin sensitivity and glucagon secretion.
- **β cell**: Regulation of insulin biosynthesis, proliferation, and apoptosis.
PREVIOUS STUDIES ON GLP-1 AGONISTS

- GLP-1 infusion ↓ basal/arginine induced glucagon secretion in T1D(1).
- Study by Rother et al, Exenatide after a meal shows ↓ in increase of glucagon (2).
- Retrospective study in obese insulin-requiring T2D, Exenatide showed ↓ CRP, TG, SBP, mean Hba1c & Insulin dose (Rapid acting & mixed-type) (3).

LIRAGLUTIDE

- Human Glucagon Like Peptide (GLP-1) Analogue
- Incretin mimetic.
- Bioavailability 55%.
- Peak Plasma Time: 8-12 Hrs. Half-life: 13 Hrs
- Protein Bound: >98%.
- Endogenously Metabolized Without A Specific Organ Route.
  - Pharmacokinetics + Dynamics - Duration Of Action Of 24 Hours.
- Excretion: Feces (5%), Urine (6%)
DEXCOM G4 CONTINUOUS GLUCOSE MONITORING SYSTEM

Dexcom G4 Receiver

Dexcom G4 Transmitter

Dexcom G4 Sensor
WEEKLY CGM RECORD OF T1D BEFORE /AFTER LIRAGLUTIDE
PRELIMINARY STUDY (4)

- Diabetes-Endocrinology Center of WNY.

- Nonrandomized study In well-controlled and thin T1D.

- 14 pts (9M, 5F) T1D (c-peptide < 0.10 nmol/L, GAD+) on CGM.

- pts improved glycemic control by greater attention to BG, dietary intake, carb counting, adjusting insulin dose, exercise.

- Target premeal glucose 80–120 mg/dl, 2H postmeal glucose <140 mg/dl.

- minimize hyperglycemic excursions to achieve mean BG <130 mg/dl.

CONCLUSIONS OF PRELIMINARY STUDY

- Significant decrease in
  - mean weekly glucose concentration.
  - mean Hba1c.
  - SD of glucose readings.
  - basal / bolus / total insulin requirement.

- ↓ appetite / weight loss.
- unchanged c-peptide levels (? suppression of glucagon).
- improved glucose homeostasis  ? ↓ carb intake vs. slower gastric emptying.
- when Liraglutide stopped, original doses of insulin restored.
- glycemic excursions returned in a similar period (Reversibility)
Varanasi et al - nonrandomized study in well-controlled, thin T1D.

Observations made in well-controlled T1D who continued to have significant BG oscillations despite insulin dose adjustments.

Benefits were then demonstrated in poorly controlled & obese T1D. (5)

Kuhadiya et al - nonrandomized study in poorly controlled, obese T1D.

Both were done at Diabetes Endocrinology Center of WNY.

LIMITATIONS OF PRELIM STUDIES

- not placebo controlled.
- not double blinded.
- not generalizable – pts selected were well controlled (based on Hba1c).

OUTCOME OF PRELIM STUDIES

- initial proof for future placebo- controlled, double blind trial.
HYPOTHESIS

- **Hypothesis 1:** Liraglutide ↓ Fasting, Postprandial, mean glucose conc In T1D.
  - Compare Hba1c, mean fasting/weekly glucose, SD of weekly glucose (using CGM) & Insulin required before / after 52 wks of Liraglutide Rx.

- **Hypothesis 2:** Liraglutide ↓ postprandial glucagon conc *(Meal Challenge)*

- **Hypothesis 3:** Liraglutide ↑ postprandial c-peptide conc *(Meal Challenge)*

- **Hypothesis 4:** Delays gastric emptying *(Acetaminophen Absorption)*
NOVELTY

- First Study To Investigate Effect of Liraglutide on glycemic levels / variability In T1D on Insulin.
- First study to investigate Role of Glucagon.
- Potential Basal / Postprandial glucagon suppression by Liraglutide.
- Using CGM to assess rapidity / consistency of response to Liraglutide.
- can Liraglutide activate Dormant B–cells?
RESEARCH DESIGN & METHODS

- prospective, randomized, double blind, placebo controlled study first 6m.
- open label study next 6 months.
- conducted at Diabetes Endocrinology Center of WNY (SUNY buffalo).
- funded by endocrine fellows foundation grant.
STUDY POPULATION

- 96 T1D on Insulin pump or multiple injections of insulin per day included.
- Randomized to 2 groups - placebo or 1.8 mg Liraglutide daily.
- To avoid hypoglycemia / nausea, pts started on 0.6 mg Liraglutide per day, titrated up to 1.2 mg, then 1.8 mg over 4-5 weeks based on Tolerability.
INCLUSION CRITERIA

- T1D: fasting c-peptide < 0.1nmol/l
- on insulin therapy >12 months with/without Hx of DKA.
- regularly measure BG 4 times daily.
- insulin pump or multiple (>4) injections of insulin / day
- Hba1c < 10%.
- well versed with carb counting.
- age 30-75 years.
- BMI 20-40 kg/m2.
EXCLUSION CRITERIA

- T1D < 12 m.
- coronary event or any life-threatening, non-cardiac disease.
- hepatic disease, renal impairment (Cr > 1.5)
- HIV / hep C positive status.
- Hx pancreatitis, gastroparesis, medullary thyroid carcinoma, MEN 2.
- pregnancy
- inability to give informed consent
- FHx MEN 2, medullary thyroid cancer.
POSSIBLE RISKS TO THE SUBJECT

- hypoglycemia
- nausea / vomiting
- pancreatitis
- medullary thyroid cancer
- hypersensitivity
- pts asked to maintain diary to record hypoglycemia / side effects.
STUDY DESIGN

SCREENING DAY-
- History & physical exam
- Informed consent
- Fasting baseline labs - CBC, CMP, HBA1C, Lipid Profile

RANDOMIZATION METHOD

After screening visit, subjects who meet criteria are assigned a random number using Microsoft excel
<table>
<thead>
<tr>
<th>GLYCEMIC INDICES</th>
<th>LIRAGLUTIDE</th>
<th>PLACEBO</th>
<th>P VALUE (T-TEST)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>48 ± 3</td>
<td>46 ± 4</td>
<td>P = 0.87</td>
</tr>
<tr>
<td>Age of T1D diagnosis</td>
<td>19 ± 2</td>
<td>18 ± 3</td>
<td>P = 0.42</td>
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<tr>
<td>HbA1c</td>
<td>8.11 ± 0.8</td>
<td>7.49 ± 0.80</td>
<td>P = 0.08</td>
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<tr>
<td>Weekly Average Glucose level (mg/dl)</td>
<td>174.6 ± 33.7</td>
<td>163.7 ± 29.2</td>
<td>P = 0.42</td>
</tr>
<tr>
<td>Weekly Average Fasting level (mg/dl)</td>
<td>162.5 ± 37.1</td>
<td>177.5 ± 33.5</td>
<td>P = 0.46</td>
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<tr>
<td>Weekly Basal Insulin dose</td>
<td>27.6 ± 10.1</td>
<td>26.0 ± 21.3</td>
<td>P = 0.82</td>
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<tr>
<td>Weekly Bolus Insulin dose</td>
<td>25.2 ± 14.9</td>
<td>22.6 ± 16.4</td>
<td>P = 0.86</td>
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<tr>
<td>Weekly Total Insulin dose</td>
<td>52.7 ± 22.3</td>
<td>50.1 ± 39.0</td>
<td>P = 0.84</td>
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<tr>
<td>Weekly Carbohydrate Intake (g)</td>
<td>162.2 ± 91.9</td>
<td>167.6 ± 57.9</td>
<td>P = 0.44</td>
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<tr>
<td>Time spent in Hypoglycemia (&lt; 55 )</td>
<td>4.6 ± 6.2</td>
<td>7.5 ± 14.0</td>
<td>P = 0.014</td>
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<tr>
<td>Time spent in Hypoglycemia (≥55 - &lt;70)</td>
<td>4.8 ± 5.6</td>
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<td>P = 0.88</td>
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<tr>
<td>Time spent in Normoglycemia (≥70-≤160)</td>
<td>36.3 ± 15.4</td>
<td>41.9 ± 13.6</td>
<td>P = 0.36</td>
</tr>
<tr>
<td>Time spent in Hyperglycemia (&gt;160-≤240)</td>
<td>32.0 ± 10.1</td>
<td>29.3 ± 5.5</td>
<td>P = 0.44</td>
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<tr>
<td>Time spent in Hyperglycemia (&gt;240)</td>
<td>22.3 ± 14.4</td>
<td>16.6 ± 12.1</td>
<td>P = 0.33</td>
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<tr>
<td>Weight (lbs)</td>
<td>186.3 ± 27.4</td>
<td>177.3 ± 60.1</td>
<td>P = 0.65</td>
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<tr>
<td>BMI</td>
<td>29.51 ± 4.0</td>
<td>26.53 ± 4.5</td>
<td>P = 0.11</td>
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<td>SBP (mm Hg)</td>
<td>131.7 ± 12.3</td>
<td>124.6 ± 12.5</td>
<td>P = 0.19</td>
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</table>
PRE-STUDY PHASE

- registered dietitian - carb counting.
- CGM insertion, pt blinded to CGM.
- check BG by fingerstick before & 2hr after each meal.
- Food dairy - calorie intake.
- pts on Insulin pump use bolus wizard.
- Target glucose
  - pre-prandial 80-120mg/dl.
  - 2h postprandial < 140mg/dl.
  - avoid blood glucose < 70mg/dl.
- Adjustments to insulin doses by study investigator based on CGM data.
STUDY VISIT DAY 0

- patient fasting.
- 24 hour urine sample.
- CGM data to assess glycemic control before Liraglutide Rx.
- Meal challenge test.
- Injection technique for Liraglutide.
- Start Liraglutide at 0.6 mg/day or placebo.
STUDY VISIT WEEK 8, 12, 16, 20, 24

- Fingerstick / CGM data since last visit collected.
- Insulin dose adjusted by study investigator to optimize BG control.
- Hba1c checked Q3 monthly.
- if Hba1c < 7.0%, ↓ dose of basal/bolus insulin by 25%.
- if Hba1c > 7.5%, no change.
- Hba1c 7.0 - 7.5%, ↓ dose by 10% (based on prelim data).
STUDY VISIT WEEK 26

- two questionnaires
  - DSQOLS (diabetes specific quality of life scale).
  - PAID (problem areas in diabetes survey).
- pts on placebo now receive Liraglutide for remaining 26 weeks.

WEEK 32, 36, 40, 44, 48 & 52

- insulin dose adjusted to optimize blood sugar control.
- fasting blood sample at week 52 to measure inflammatory mediators.
# Flow Chart of Study Procedures

<table>
<thead>
<tr>
<th></th>
<th>H&amp; P</th>
<th>CBC/CMP</th>
<th>Preg test</th>
<th>HbA1c</th>
<th>blood test</th>
<th>meal challenge</th>
<th>CGM insertion</th>
<th>dietician</th>
<th>CDE for CGM insertion or pen teaching</th>
<th>24 hour urine</th>
<th>collect CGM data, adjust insulin</th>
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</table>
MEAL CHALLENGE TEST

- on day 0 & week 52
- 910 calorie high fat / carb meal.
- pre meal insulin individualized based on I : C ratio / Correction Factor
- Acetaminophen (based on body wt) ingested before meal.
- blood acetaminophen levels checked at intervals to assess rate of gastric emptying
- Liraglutide injected on week 52 (45 min prior to meal).
- sequential blood samples at 0, 15, 30, 45, 60, 90, 120, 150, 180, 210, 240 & 300 min
To detect a difference in glycemic indices after Rx with Liraglutide vs. Placebo at 0.05 level.

- Hba1c, weekly avg glucose, weekly avg fasting glucose.
- weekly basal / bolus / total insulin dose.
- weekly carb intake (g) / helpings.
- time spent in hypo / normo / hyperglycemia.
- c-peptide, glucagon, GLP-1, GIP conc.
- Area under curve of glucose conc. after meal challenge.
STATISTICAL ANALYSIS

SECONDARY ENDPOINT

To detect a difference in non glycemic indices after Liraglutide vs. Placebo at 0.05 level.

- weight/BMI, SBP/DBP, HR.
- gastric emptying.
QUARTERLY ANALYSIS

- Recruited 22 patients (11 study drug, 11 placebo)
- Data unblinded for Q analysis.
- Paired t-test (2 tailed) - before / after comparisons of avgs of glycemic & non glycemic indices in placebo & Rx groups [http://vassarstats.net/tu.html](http://vassarstats.net/tu.html).
- Unpaired t-test - compare delta change avgs of glycemic & non glycemic indices between placebo vs. Rx groups.
## Q ANALYSIS (LIRAGLUTIDE N=11)

<table>
<thead>
<tr>
<th>GLYCEMIC INDICES</th>
<th>WEEK 0</th>
<th>WEEK 12</th>
<th>P VALUE (T-TEST)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>8.11 ± 0.8</td>
<td>7.44 ± 0.8</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>Weekly Average Glucose level (mg/dl)</td>
<td>174.6 ± 33.7</td>
<td>147.4 ± 21.6</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>Weekly Average Fasting level (mg/dl)</td>
<td>162.5 ± 37.1</td>
<td>123.8 ± 24.7</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>Weekly Basal Insulin dose</td>
<td>27.6 ± 10.1</td>
<td>24.4 ± 9.3</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>Weekly Bolus Insulin dose</td>
<td>25.2 ± 14.9</td>
<td>20.4 ± 11.8</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>Weekly Total Insulin dose</td>
<td>52.7 ± 22.3</td>
<td>45.5 ± 17.9</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>Weekly Carbohydrate Intake (g)</td>
<td>162.2 ± 91.9</td>
<td>139.4 ± 75.4</td>
<td>P = 0.076</td>
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<tr>
<td>Weekly Carbohydrate helpings</td>
<td>3.5 ± 1.1</td>
<td>2.9 ± 0.9</td>
<td>P &lt; 0.05</td>
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<tr>
<td>Time spent in Hypoglycemia (&lt; 55 )</td>
<td>4.6 ± 6.2</td>
<td>4.3 ± 4.6</td>
<td>P = 0.80</td>
</tr>
<tr>
<td>Time spent in Hypoglycemia (≥55 - &lt;70 )</td>
<td>4.8 ± 5.6</td>
<td>3.9 ± 2.2</td>
<td>P = 0.45</td>
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<tr>
<td>Time spent in Normoglycemia (≥70-≤160 )</td>
<td>36.3 ± 15.4</td>
<td>49.7 ± 17.2</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>Time spent in Hyperglycemia (&gt;160-≤ 240)</td>
<td>32.0 ± 10.1</td>
<td>25.7 ± 9.4</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>Time spent in Hyperglycemia ( &gt;240 )</td>
<td>22.3 ± 14.4</td>
<td>10.2 ± 5.3</td>
<td>P &lt; 0.05</td>
</tr>
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</table>
## Q ANALYSIS (PLACEBO N=11)

<table>
<thead>
<tr>
<th>GLYCEMIC INDICES</th>
<th>WEEK 0</th>
<th>WEEK 12</th>
<th>P VALUE (T-TEST)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>7.49 ± 0.80</td>
<td>7.25 ± 0.70</td>
<td>P = 0.057</td>
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<tr>
<td>Weekly Average Glucose level (mg/dl)</td>
<td>163.7 ± 29.2</td>
<td>171.5 ± 31.1</td>
<td>P = 0.26</td>
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<tr>
<td>Weekly Average Fasting level (mg/dl)</td>
<td>177.5 ± 33.5</td>
<td>170.3 ± 39.2</td>
<td>P = 0.70</td>
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<tr>
<td>Weekly Basal Insulin dose</td>
<td>26.0 ± 21.3</td>
<td>27.2 ± 20.9</td>
<td>P = 0.30</td>
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<tr>
<td>Weekly Bolus Insulin dose</td>
<td>22.6 ± 16.4</td>
<td>20.9 ± 12.3</td>
<td>P = 0.35</td>
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<tr>
<td>Weekly Total Insulin dose</td>
<td>50.1 ± 39.0</td>
<td>50.5 ± 36.1</td>
<td>P = 0.79</td>
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<tr>
<td>Weekly Carbohydrate Intake (g)</td>
<td>167.6 ± 57.9</td>
<td>162.2 ± 63.8</td>
<td>P = 0.65</td>
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<tr>
<td>Weekly Carbohydrate helpings</td>
<td>1.1 ± 0.4</td>
<td>1.2 ± 0.5</td>
<td>P = 0.44</td>
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<tr>
<td>Time spent in Hypoglycemia (&lt; 55 )</td>
<td>7.5 ± 14.0</td>
<td>6.7 ± 16.1</td>
<td>P = 0.61</td>
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<td>Time spent in Hypoglycemia (≥55 - &lt;70 )</td>
<td>4.5 ± 2.3</td>
<td>2.5 ± 1.6</td>
<td>P &lt; 0.05</td>
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<tr>
<td>Time spent Normoglycemia (≥70 - ≤160 )</td>
<td>41.9 ± 13.6</td>
<td>43.9 ± 13.9</td>
<td>P = 0.28</td>
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<tr>
<td>Time spent Hyperglycemia (&gt;160 - ≤240)</td>
<td>29.3 ± 5.5</td>
<td>25.9 ± 4.4</td>
<td>P = 0.17</td>
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<tr>
<td>Time spent in Hyperglycemia (&gt;240 )</td>
<td>16.6 ± 12.1</td>
<td>21.9 ± 19.3</td>
<td>P = 0.24</td>
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### Q ANALYSIS (LIRAGLUTIDE N=11)

<table>
<thead>
<tr>
<th>NON GLYCEMIC INDICES</th>
<th>WEEK 0</th>
<th>WEEK 12</th>
<th>P VALUE (T-TEST)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (lbs)</td>
<td>186.3 ± 27.4</td>
<td>178.1 ± 29.9</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>BMI</td>
<td>29.51 ± 4.0</td>
<td>27.98 ± 4.0</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>131.7 ± 12.3</td>
<td>125.1 ± 10.5</td>
<td>P = 0.14</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>81.0 ± 7.6</td>
<td>81.2 ± 9.0</td>
<td>P = 0.94</td>
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<tr>
<td>Pulse Rate</td>
<td>78.7 ± 9.6</td>
<td>75.4 ± 7.5</td>
<td>P = 0.32</td>
</tr>
</tbody>
</table>

### Q ANALYSIS (PLACEBO N=11)

<table>
<thead>
<tr>
<th>NON GLYCEMIC INDICES</th>
<th>WEEK 0</th>
<th>WEEK 12</th>
<th>P VALUE (T-TEST)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (lbs)</td>
<td>177.3 ± 60.1</td>
<td>175.7 ± 59.5</td>
<td>P = 0.12</td>
</tr>
<tr>
<td>BMI</td>
<td>26.53 ± 4.5</td>
<td>26.35 ± 4.9</td>
<td>P = 0.44</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>124.6 ± 12.5</td>
<td>124.3 ± 15.3</td>
<td>P = 0.90</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>74.9 ± 6.1</td>
<td>75.1 ± 5.6</td>
<td>P = 0.91</td>
</tr>
<tr>
<td>Pulse Rate</td>
<td>74.2 ± 11.1</td>
<td>70.0 ± 12.2</td>
<td>P = 0.26</td>
</tr>
<tr>
<td><strong>Δ INDICES</strong></td>
<td><strong>PLACEBO</strong></td>
<td><strong>LIRAGLUTIDE</strong></td>
<td><strong>P VALUE (T-TEST)</strong></td>
</tr>
<tr>
<td>--------------------------------------------------</td>
<td>--------------</td>
<td>-----------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Δ HbA1c</td>
<td>-0.24 ± -0.10</td>
<td>-0.67 ± -0.07</td>
<td>P = 0.07</td>
</tr>
<tr>
<td>Δ Weekly Average Glucose level (mg/dl)</td>
<td>7.7 ± 1.9</td>
<td>-27.3 ± -12.1</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>Δ Weekly Average Fasting level (mg/dl)</td>
<td>-7.2 ± -17.8</td>
<td>-38.6 ± -12.5</td>
<td>P = 0.16</td>
</tr>
<tr>
<td>Δ Weekly Basal Insulin dose</td>
<td>1.3 ± -0.4</td>
<td>-3.2 ± -0.8</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>Δ Weekly Bolus Insulin dose</td>
<td>-1.7 ± -4.1</td>
<td>-4.8 ± -3.0</td>
<td>P = 0.23</td>
</tr>
<tr>
<td>Δ Weekly Total Insulin dose</td>
<td>0.4 ± -2.8</td>
<td>-7.3 ± -4.4</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>Δ Weekly Carbohydrate Intake (g)</td>
<td>-5.4 ± 5.91</td>
<td>-22.8 ± -16.56</td>
<td>P = 0.3</td>
</tr>
<tr>
<td>Δ Weekly Carbohydrate helpings</td>
<td>0.11 ± 0.05</td>
<td>-0.61 ± -0.18</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>Δ Time spent in Hypoglycemia (&lt; 55 )</td>
<td>-0.8 ± 2.1</td>
<td>-0.4 ± -1.5</td>
<td>P = 0.83</td>
</tr>
<tr>
<td>Δ Time spent in Hypoglycemia (≥55 - &lt;70)</td>
<td>-2.0 ± -0.7</td>
<td>-0.9 ± -3.4</td>
<td>P = 0.43</td>
</tr>
<tr>
<td>Δ Time spent Normoglycemia (≥70 - ≤160 )</td>
<td>2.0 ± 0.3</td>
<td>13.5 ± 1.7</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>Δ Time spent Hyperglycemia (&gt;160 - ≤240)</td>
<td>-3.4 ± 1.1</td>
<td>-6.3 ± -0.7</td>
<td>P = 0.32</td>
</tr>
<tr>
<td>Δ Time spent Hyperglycemia (&gt;240 )</td>
<td>5.3 ± 7.2</td>
<td>-12.1 ± -9.1</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>Δ Weight (lbs)</td>
<td>1.5 ± -0.6</td>
<td>-8.1 ± 2.5</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>Δ BMI</td>
<td>-0.18 ± 0.37</td>
<td>-1.54 ± -0.02</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>Δ SBP (mm Hg)</td>
<td>-0.3 ± 2.8</td>
<td>-6.6 ± -1.8</td>
<td>P = 0.23</td>
</tr>
<tr>
<td>Δ DBP (mm Hg)</td>
<td>0.2 ± -0.5</td>
<td>0.2 ± 1.4</td>
<td>P = 0.99</td>
</tr>
<tr>
<td>Δ Pulse Rate</td>
<td>-4.8 ± 1.13</td>
<td>-3.81 ± -2.25</td>
<td>P = 0.94</td>
</tr>
</tbody>
</table>
AFTER ADDING LIRAGLUTIDE

- significant decrease in
  - mean avg BG
  - mean fasting BG
  - mean Hba1c
  - SD of BG readings
  - dose of basal / bolus / total insulin required.
  - time spent in hyperglycemia (> 160).

- significantly increased time spent in normoglycemia (70 – 160).
AFTER ADDING LIRAGLUTIDE

- ↓ appetite (based on carb helpings)
- ↓ body wt

- Despite reduction in insulin dose.
  - ↓ mean weekly glucose conc.
  - ↓ time spent in hyperglycemia.
  - ↓ BG oscillations (peaks / troughs) (↓ mean SD)
CONCLUSION

- quick improvement in glycemic control (in 1 week)
  - cannot be attributed to wt loss
  - ? insulin sensitization
- \( \downarrow \) insulin requirement ? insulin sensitization
- improved glucose homeostasis ? \( \downarrow \) carb intake vs. slower gastric emptying
- slower gastric emptying \( \downarrow \) post meal BG excursion (does not explain \( \downarrow \) fasting BG)
FUTURE STUDY GOALS

- **inflammatory cytokines** interfere with insulin signal transduction (6).
- Liraglutide may have an anti-inflammatory effect.
- Suppression of cytokines - ? insulin sensitization / ↓ insulin resistance.
- Potentially anti-atherogenic (atherosclerosis is chronic inflammatory process)

FUTURE STUDY GOALS

- long standing T1D have a significant **B-cell population** that is **not fully differentiated** (7-9).

- long-term Liraglutide Rx may **facilitate full differentiation** of these cells and restore some insulin secretion.

- **wt loss / appetite suppression** (important 40–50% T1D have metabolic syndrome) (10)

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REFERENCES


