Insulin and Glucagon Co-Administration in Type 1 Diabetes Prevents Hypoglycemia without Worsening Hyperglycemia

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Rationale

Hypoglycemia remains the greatest obstacle that prevents insulin-treated patients from attaining acceptable metabolic control and this, in turn, drives long term health consequences.

Insulin and glucagon are islet hormones that are thought to exert opposing glucoregulatory actions, yet there is increasing recognition that the hormones have a more complex and complementary relationship that is also glucose-dependent.

Novel findings from Vanderbilt University have demonstrated that it may be feasible to simultaneously administer both peptide hormones at such concentrations that ambient glycemia dictates the dominance of one hormone's actions over the other. In other words, it may be feasible to simultaneously co-administer the peptide hormones within certain plasma concentration conditions, allowing the control of excessive hyperglycemic and hypoglycemic excursions.

We aimed to study this concept in human subjects with Type 1 Diabetes in a controlled acute IV infusion study.

Methods

We studied Type 1 Diabetes subjects with the following inclusion criteria:

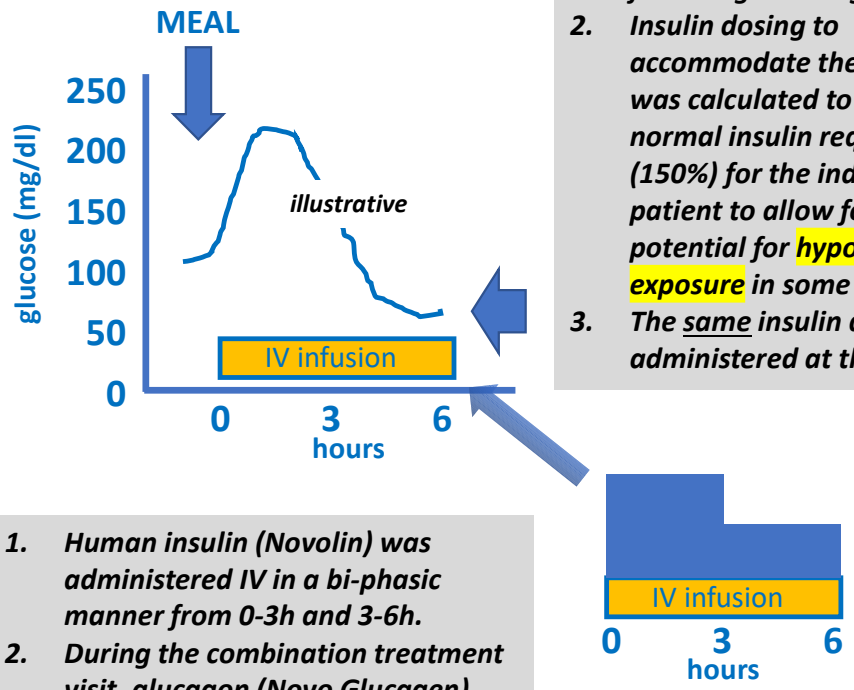
- **Aged 18-64 years**
- **Treated with insulin ≥ 12mo prior**
- **Stable insulin R_x ≥ 3mo prior**
- **Stable glycemic control with HbA1c <9.0 %**
- **C-Peptide <=0.30 nmol/L**
- **BMI <30.0 kg/m^2**

In randomized order, the two visits involved IV administration of either:

- **Insulin alone**, or
- **Insulin + Glucagon**

Subjects received a mixed meal challenge (100g CHO, Vanilla Boost) and were observed for 6h.

Mixed meal challenge ingested at <u>Time 0</u> to allow a natural rise then fall in plasma glucose over the 6h period of study.



1. ***Overnight insulin was administered (IV) to optimize study conditions for the following morning.***
2. ***Insulin dosing to accommodate the mixed meal was calculated to increase normal insulin requirements (150%) for the individual patient to allow for the potential for hypoglycemia exposure in some subjects.***
3. ***The <u>same</u> insulin dose was administered at the two visits.***

1. ***Human insulin (Novolin) was administered IV in a bi-phasic manner from 0-3h and 3-6h.***
2. ***During the combination treatment visit, glucagon (Novo Glucagen) was also administered IV in a similar fashion at a pre-determined <u>fixed insulin:glucagon molar ratio</u>.***

Patient Characteristics (n=11)

Parameter	Measure
Age (yr)	36±4
Sex (M/F)	5/6
BMI (kg/m^2)	25.0±0.7
A1C (%)	7.0±0.3
Disease duration (yr)	23±3
Daily insulin dose (u)	43±3
Regime (MDI/CSII)	3/8

Study treatment was well tolerated in all subjects, and no SAEs were reported.

Plasma insulin and glucagon levels changed in accordance with the study conditions with ambient insulin levels identical for the two study visits.

Results: Glycemic Indices

No difference in plasma glucose rise and time in range#

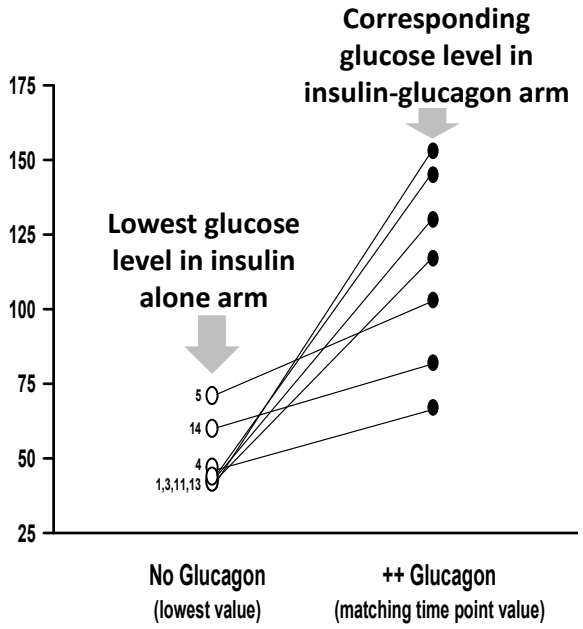
Plasma Glucose Rise	Insulin Alone	Insulin-Glucagon
Fasting PG (mg/dl)	121±5	119±6
Peak PG (mg/dl)	224±18	228±15
ΔPG 0-120$_{AUC}$ (mg.min/dl)	8,162±1516	7,871±927
ΔPG 0-180$_{AUC}$ (mg.min/dl)	10,501±3014	11,536±1,778
Time in range (70-180 mg/dl)	40%	55%

7/11 subjects experienced an excessive lowering in plasma glucose (<80 mg/dl)

Plasma Glucose Decline	Insulin Alone	Insulin-Glucagon
Time <70 mg/dl	20±7%	9±4%*
PG nadir (mg/dl)	51.1±4.0	114.0±12.0**
Requiring IV glucose rescue	5/11	2/11

Insulin:Glucagon combination conferred protection against hypoglycemia in <u>all</u> 7 cases

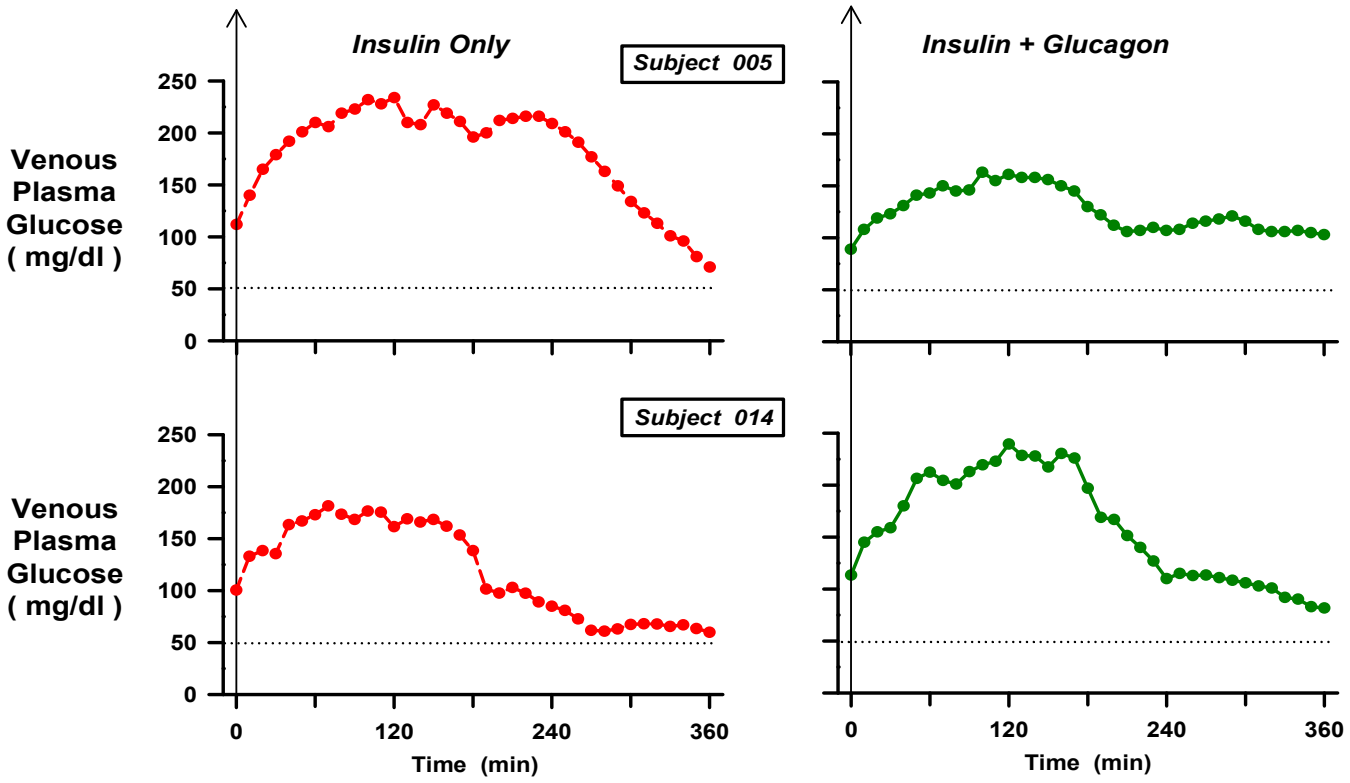
Plasma Glucose Nadir
in the n=7/11 subjects who experienced low plasma glucose during the meal challenge



#no statistical significance between treatment arms (n=11)
*statistical significance p=0.013 between treatment arms (n=11)
**statistical significance p=0.007 between treatment arms (n=7)

Results: Individual Plots

2 of 7 hypoglycemic cases



Insulin alone:
- ❑ end PG ~70mg/dl

Insulin-Glucagon
- ❑ end PG ~100 mg/dl

Insulin alone:
- ❑ end PG ~60mg/dl

Insulin-Glucagon
- ❑ end PG ~85 mg/dl

PG, plasma glucose

Results: Individual Plots

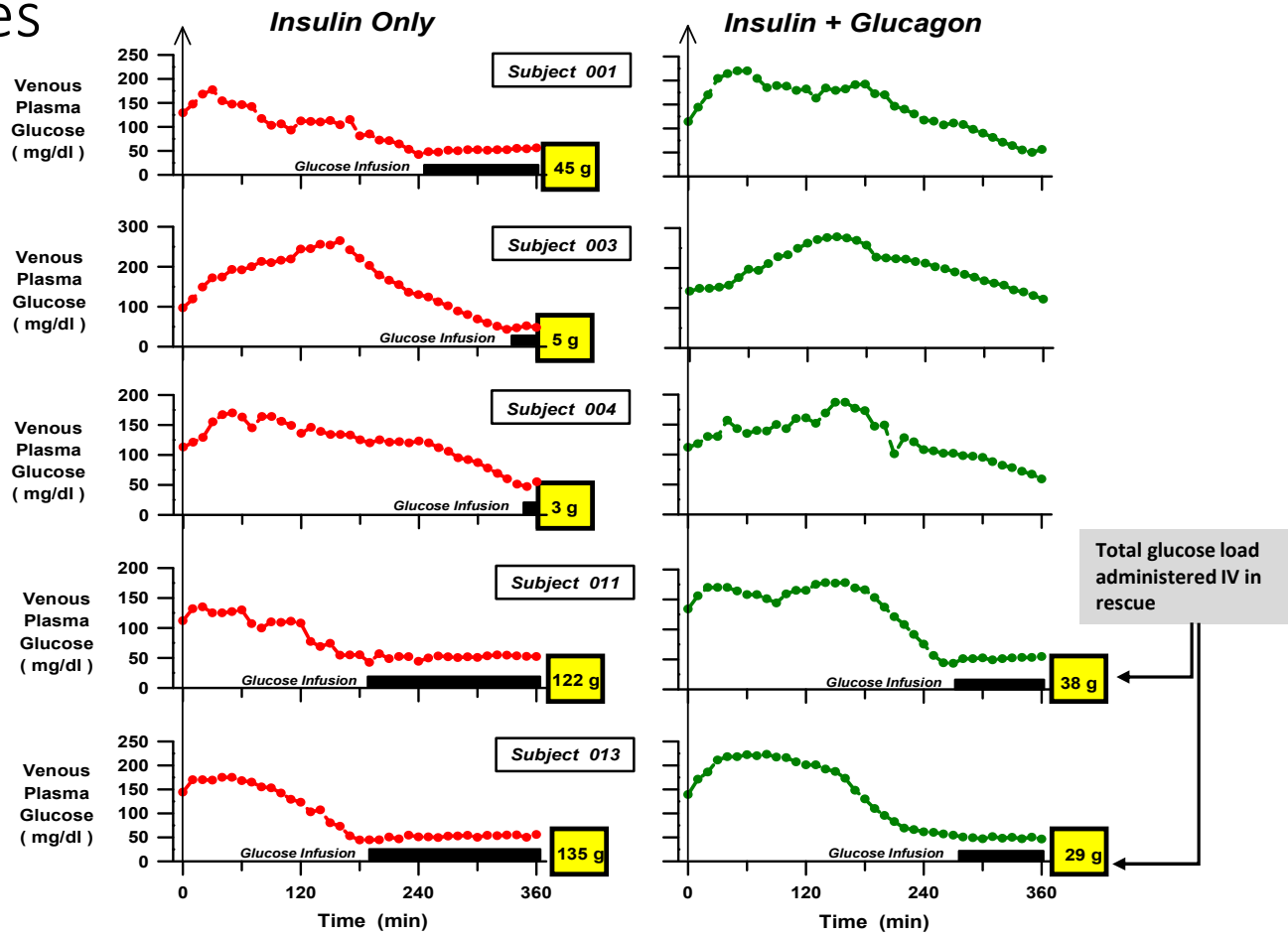
5 of 7 hypoglycemic cases

Insulin alone:

- ❑ 5 cases required IV glucose rescue in latter phase of meal period

Insulin-Glucagon:

- ❑ 2 cases received IV glucose rescue but it was initiated later in the observation period, and required much less IV glucose dose as rescue
- ❑ 3 cases **did not** require IV glucose rescue



Conclusion

We co-administered (IV) insulin and glucagon at a fixed molar ratio in subjects with Type 1 diabetes during a mixed meal challenge. We did not observe safety concerns and the treatment was well tolerated by all subjects.

We observed a clear mitigation of hypoglycemia risk in all subjects who experienced low blood glucose ***without*** worsening control of the post-meal plasma glucose rise.

This novel treatment approach is founded on an increased appreciation of the complex relationship of the two glucoregulatory peptides, thereby widening the therapeutic window of insulin and mitigating hypoglycemia risk, the greatest fear of patients. This opens the door to highly impactful yet simplified therapeutic approaches.