# Endogenous glucose production during hypoglycemia in patients with newly diagnosed and long-standing type 1 diabetes

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## Introduction

Long diabetes duration is a major risk factor for severe hypoglycemia in type 1 diabetes. Spontaneous recovery from hypoglycemia is driven by endogenous glucose production (EGP).

## Objective

This study compared EGP and glucagon response during hypoglycemia in 7 subjects with newly diagnosed type 1 diabetes (NDD) and 7 subjects with long-standing type 1 diabetes (LSD).

*Patient Baseline Characteristics*

| | NDD | LSD | P-Value |
|---|---|---|---|
| N | 7 | 7 | - |
| Age (years) | 43±11 | 42±12 | NS |
| BMI (kg/m²) | 23.6±1.9 | 25.0±1.9 | NS |
| HbA1c (mmol/mol) | 54.1±14.8 | 57.4±14.8 | NS |
| C-peptide (nmol/L) | 0.00-0.01 | 0.05-0.36 | <0.0001 |
| Total Daily Insulin Dose (IU) | 28.4±14 | 46.2±18 | NS |
| Diabetes Duration (years) | 2.0±1.2 | 26.7±10.7 | <0.0001 |

Data are given as mean ± SD or range (min. - max.). P<0.05 was considered statistically significant. NS, not significant.

## Methods

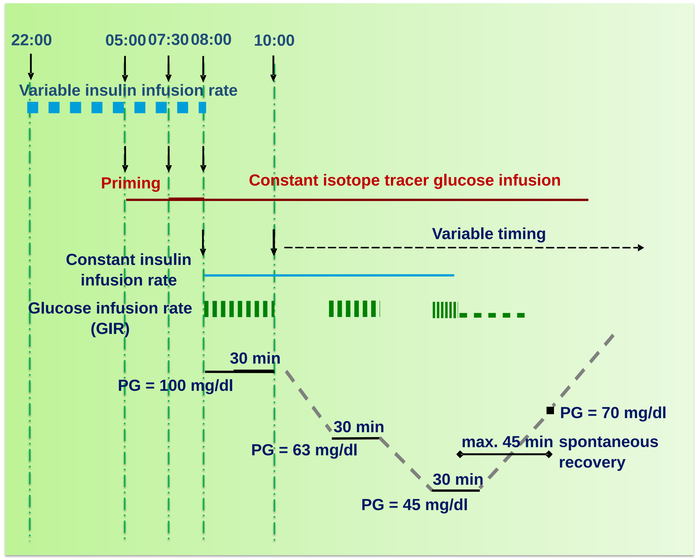
- Glucose was normalized during an overnight fast by a variable low insulin infusion.
- All subjects underwent a hyperinsulinemic stepwise hypoglycemic clamp.
- Baseline was defined as normoglycemia at low ambient insulin (low ins) in the morning, before the high insulin infusion was started.
- Plateaus were defined at 100, 63 and 45 mg/dl or when nadir was achieved.
- The recovery phase lasted from the end of the insulin infusion (15 min after achieving nadir plateau) until the end of the 70 mg/dl plateau (10 min).
- Blood samples for glucagon measurement were collected in P800 - EDTA tubes (BD, Germany) and analyzed with a solid phase two-site (high sensitive) enzyme immunoassay (Mercodia AB, Sweden).
- EGP was determined by stable isotope tracer [6, 6-$^2H_2$]-glucose technique.

**Abbreviations:**
**EGP**: endogenous glucose production
**NDD**: newly diagnosed T1D
**LSD**: long-standing T1D
**low ins**: low ambient insulin concentration
**high ins**: high ambient insulin concentration
**PG**: plasma glucose

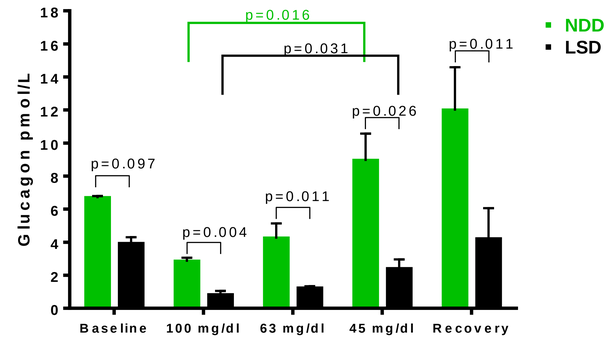
## Results

- The specific glucagon assay revealed lower glucagon concentrations than previously used assays.
- During all plateaus (100, 63 mg/dl and nadir), NDD had a significantly higher glucagon response relative to LSD.
- During the recovery phase, NDD had significantly higher glucagon levels compared to LSD.
- At plateau 100 mg/dl (high ins), both groups had a significant glucagon suppression compared to baseline.
- Both groups showed an increase of glucagon from 100 mg/dl (high ins) to nadir.

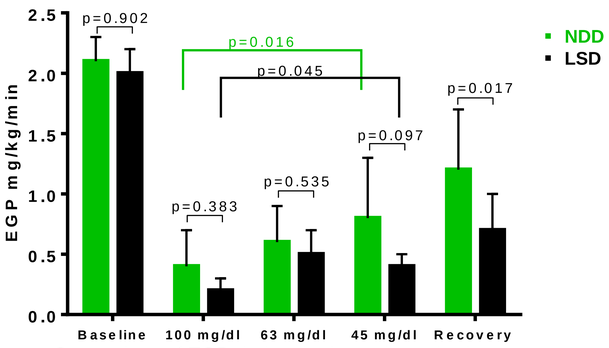
- A stable tracer enrichment was achieved in each subject.
- At baseline (low ins) and during the plateaus at 100 and 63 mg/dl, EGP suppression was comparable in both groups.
- At nadir, NDD showed a trend towards a higher EGP compared to LSD.
- During recovery, EGP was significantly higher in NDD relative to LSD.
- Both groups showed a significant increase of EGP from 100 mg/dl to nadir.




*Design of the hypoglycemic clamp and the [6,6-$^2H_2$] - glucose tracer infusion technique*




*Comparison of **glucagon** during the hypoglycemic clamp*




*Comparison of **EGP** during the hypoglycemic clamp*

## Conclusions

- The highly selective glucagon immunoassay yielded lower glucagon levels than previously used assays.
- At baseline, NDD and LSD had comparable glucagon concentrations.
- At high insulin infusion, both groups showed glucagon and EGP suppression during euglycemia.
- From 100 mg/dl to nadir, NDD and LSD had a significant increase of glucagon and hence an increase in EGP.
- NDD had a greater glucagon response during hypoglycemia and during the recovery phase compared to LSD.
- In contrast to previous studies, LSD showed a small, but significant glucagon response during hypoglycemia and recovery.
- During hypoglycemia and the recovery phase, the EGP response was associated with glucagon concentrations in both groups.