

Background and aim:

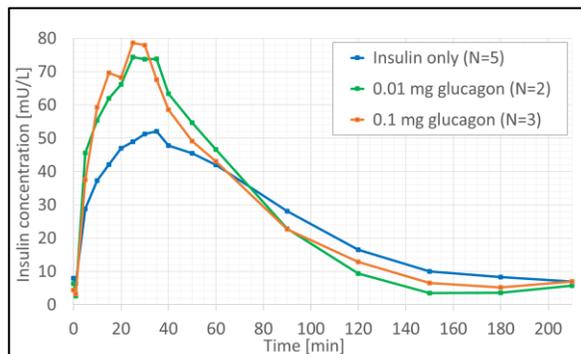
- The slow absorption and effect on glucose metabolism of SC injections of even the most fast acting meal insulins is a major challenge in the treatment of T1D.
- Among other factors absorption of SC injected insulin also depend on SC blood flow.
- Low doses of glucagon promote SC vasodilation in healthy subjects¹.
- We wanted to explore if micro-doses of glucagon enhance insulin absorption, and thus potentially would improve the performance of a bi-hormonal artificial pancreas (AP)².

Procedure: In ten anesthetized pigs, insulin and glucagon levels were suppressed by a continuous infusion of a somatostatin analogue. A continuous glucose infusion was adjusted to keep blood glucose around 5 mmol/L (euglycemic clamp). Pigs were injected with 10 IU of insulin (Lyumjev®). Half the pigs also received Glucagon® (0.1 or 0.01 mg) at the exact same SC site as insulin was injected.

Results: The effect on insulin absorption can be seen in Figure 1. During insulin-only injections C_{max} is reached at 35 minutes while in the glucagon group C_{max} is reached at 25 minutes. The insulin C_{max} after concomitant glucagon delivery was 45-50% higher than after injections with only insulin.

The effect on glucose metabolism, given as glucose infusion rate, can be seen in Figure 2. Figure 3 gives the glucagon levels after glucagon injections. Glucagon C_{max} was reached after 10 and 15 minutes with the lower and higher glucagon dose, respectively. Glucagon C_{max} with the lower glucagon dose was only 14% of C_{max} with the higher dose.

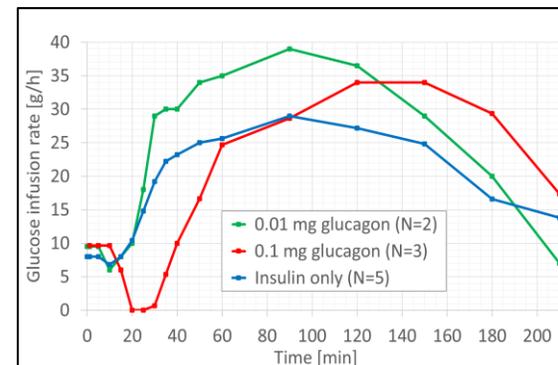
Figure 1: Insulin levels



Discussion: Low (0.1 mg) and micro-doses (0.01 mg) of glucagon enhance the absorption of SC injected insulin. The effect on insulin levels is most pronounced within the first 30 minutes and it is noteworthy that C_{max} both is reached earlier and is about 50% higher when glucagon is injected at the exact same site as SC insulin is injected.

The initial negative effect on glucose metabolism after the low-dose glucagon is not observed

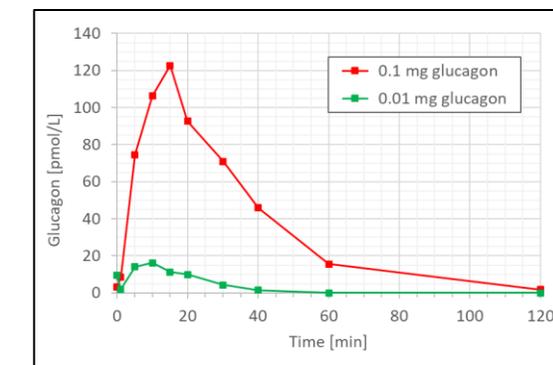
Figure 2: Glucose infusion rates



after the 0.01 mg micro-dose of glucagon. The C_{max} observed after the lower dose is also in the range observed in T1D patients 30 minutes after start of a meal³. The fact that we observe a full effect of a micro-dose of glucagon on insulin absorption without an adverse effect on glucose metabolism indicates that micro-doses of glucagon could be used in humans with T1D to enhance insulin absorption.

Conclusion: Micro-doses of glucagon enhance the absorption of even the most fast acting meal insulin (Lyumjev®) and increase the effect on glucose metabolism. Used in a bi-hormonal AP this could improve the overall glucose control and make a fully automated AP with superior glucose control possible.

Figure 3: Glucagon levels



Addendum: The effect of micro-doses of glucagon on the absorption of insulin will be studied in T1D patients during Q1-2 2023. Bi-hormonal AP experiments in T1D planned for Q3-4 2023.

References:

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