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*Hyperglycemic Clamp (HC)*  
*and*  
*Mixed Meal Tolerance*  
*(MTT) Test*

# *Background Information & Rationale*



- Insulin secretory dysfunction is a hallmark of Type 2 diabetes
- Some of the abnormalities that characterize this secretory dysfunction include a state of:
  - 1) relatively lower insulin levels
  - 2) possible reduced effect of incretins in potentiating glucose-dependent insulin secretion
- There are several methods currently in vogue which can assess different phases of insulin secretory response, however, there is no single test that can provide an assessment of both direct glycemia-dependent (GD) (but incretin-independent) as well as incretin-dependent GDIS (glucose dependant insulin secretion) in a single experiment.
- A methodology combining the hyperglycemic clamp and MTT should yield a comprehensive assessment of both the direct pancreatic as well as the incretin-based GDIS effects of novel compounds.

# *Objectives*



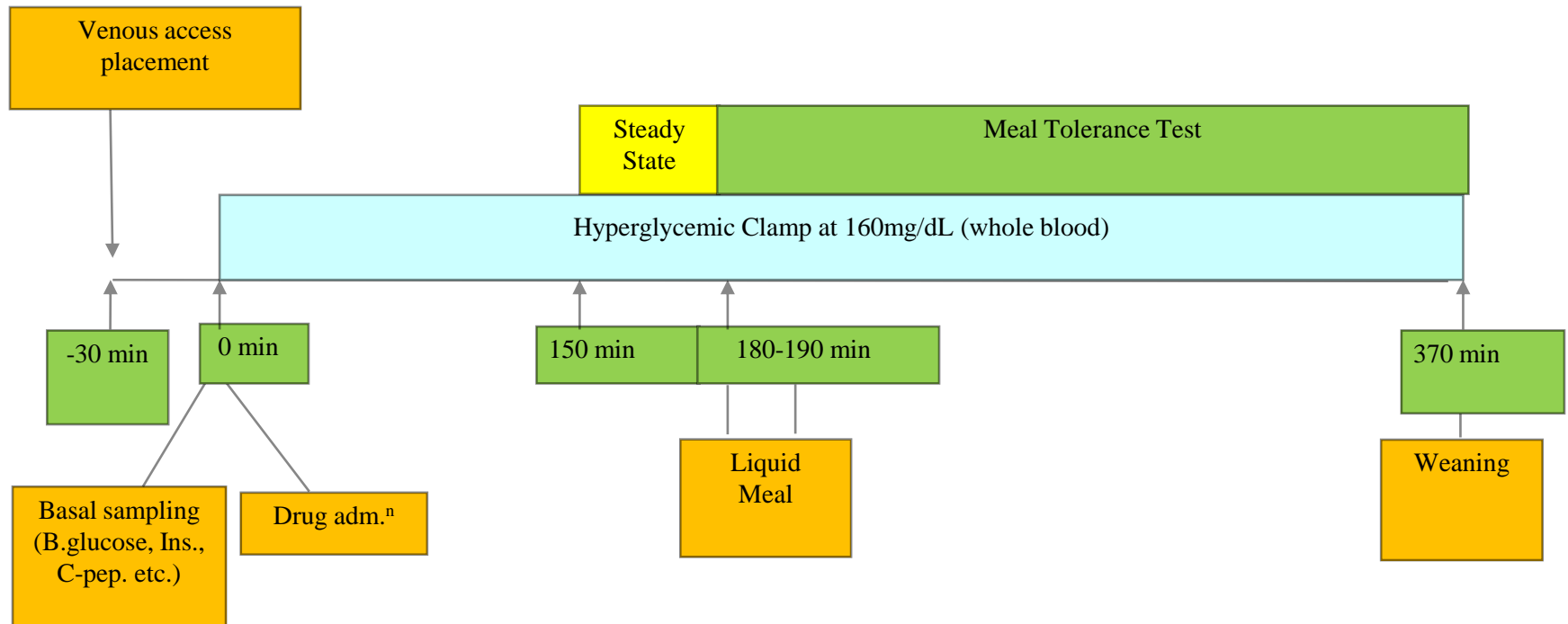
- To assess insulinotropic effects of active compound Vs placebo by estimating insulin secretion rate
- To assess effects of active compound Vs placebo on the glucose infusion rate (GIR) during a meal tolerance test (MTT) in the context of a hyperglycemic clamp (MTT-clamp).
- To assess reproducibility of the method

# *Methodology*

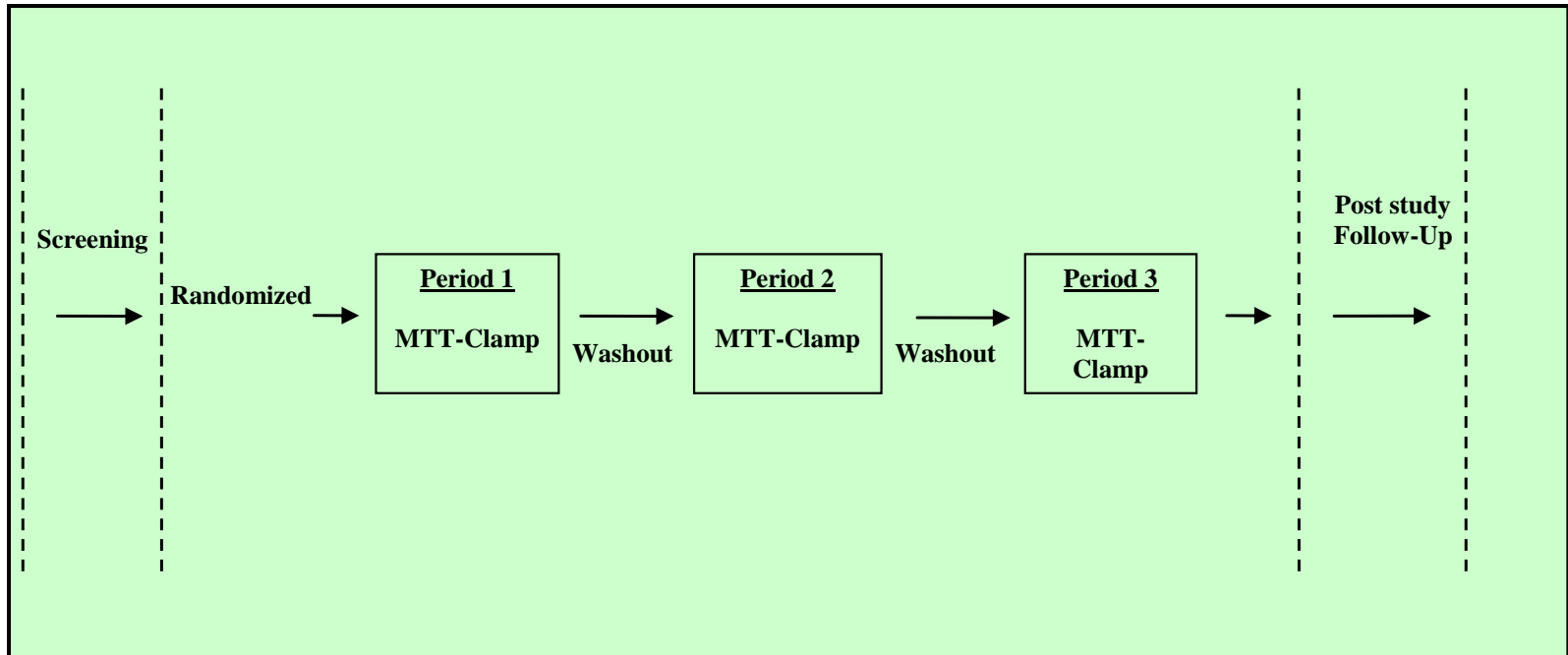


- Overnight fast for at least 10 hrs.
- Baseline blood glucose, s. insulin and c-peptide level estimation
- Drug administration (t= 0 min.)
- Priming infusion (0-15 min.) to achieve blood glucose 160 mg %
- Hyperglycemic clamp up to 180 min.
- Liquid meal over 10 min. (180-190 min.)
- Post meal clamp for 170 min (up to 360 min.)
- Blood glucose estimation every 05 min. throughout the clamp
- PK sample for Insulin, C-peptide and GLP-1 at pre defined intervals

# Methodology – Flow of events



# Study Design



# *Population*



- Healthy lean subjects with BMI 18 – 23 kg/m<sup>2</sup>
- Non-smokers
- Negative family history of T2DM.
- No other clinically significant abnormality on clinical examination/  
lab. assessment/ ECG.
- Willing to give informed consent

# Results for B.glucose

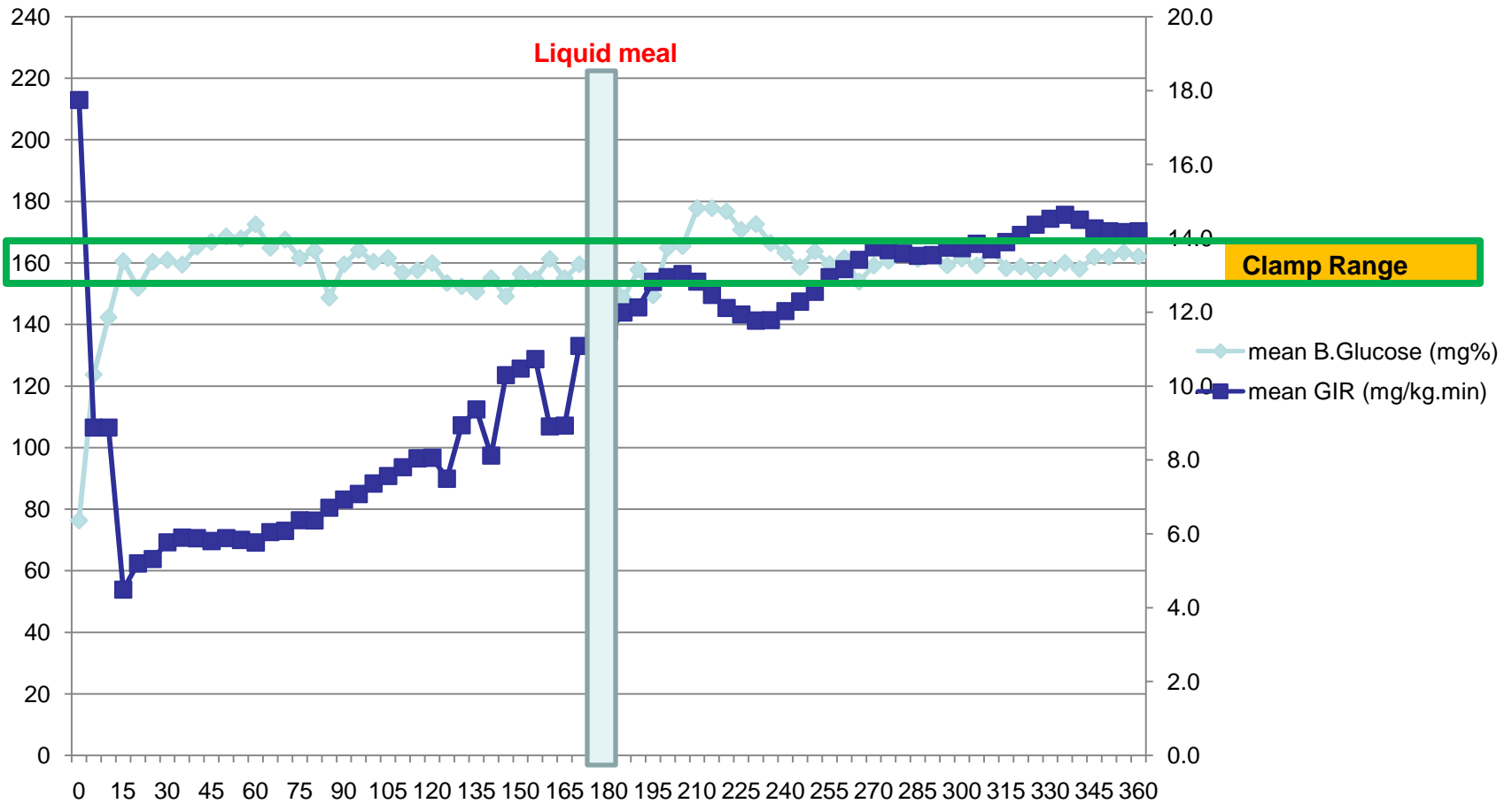


		SUB. 01	SUB. 02	SUB. 03	SUB. 04	SUB. 05	SUB. 06	SUB. 07	SUB. 08
<b>20-90 min.(HC clamp- initial)</b>	<b>Mean</b>	158.07	162.80	180.80	164.87	160.60	153.80	164.14	155.87
	<b>SD</b>	13.17	9.47	16.05	7.08	8.19	22.89	11.62	12.91
	<b>CV%</b>	8.33	5.82	8.87	4.29	5.10	14.88	7.08	8.28
<b>90-180 min (HC clamp SS)</b>	<b>Mean</b>	156.00	159.50	163.22	159.00	160.33	146.06	151.67	158.22
	<b>SD</b>	6.51	12.37	12.65	8.15	6.62	14.32	6.91	8.69
	<b>CV%</b>	4.17	7.76	7.75	5.13	4.13	9.80	4.56	5.50
<b>190-360 min. (Post meal)</b>	<b>Mean</b>	158.91	170.09	163.54	164.11	161.12	157.32	151.79	173.23
	<b>SD</b>	13.89	19.40	8.05	8.26	9.85	15.34	13.66	17.57
	<b>CV%</b>	8.74	11.40	4.92	5.04	6.11	9.75	9.00	10.14

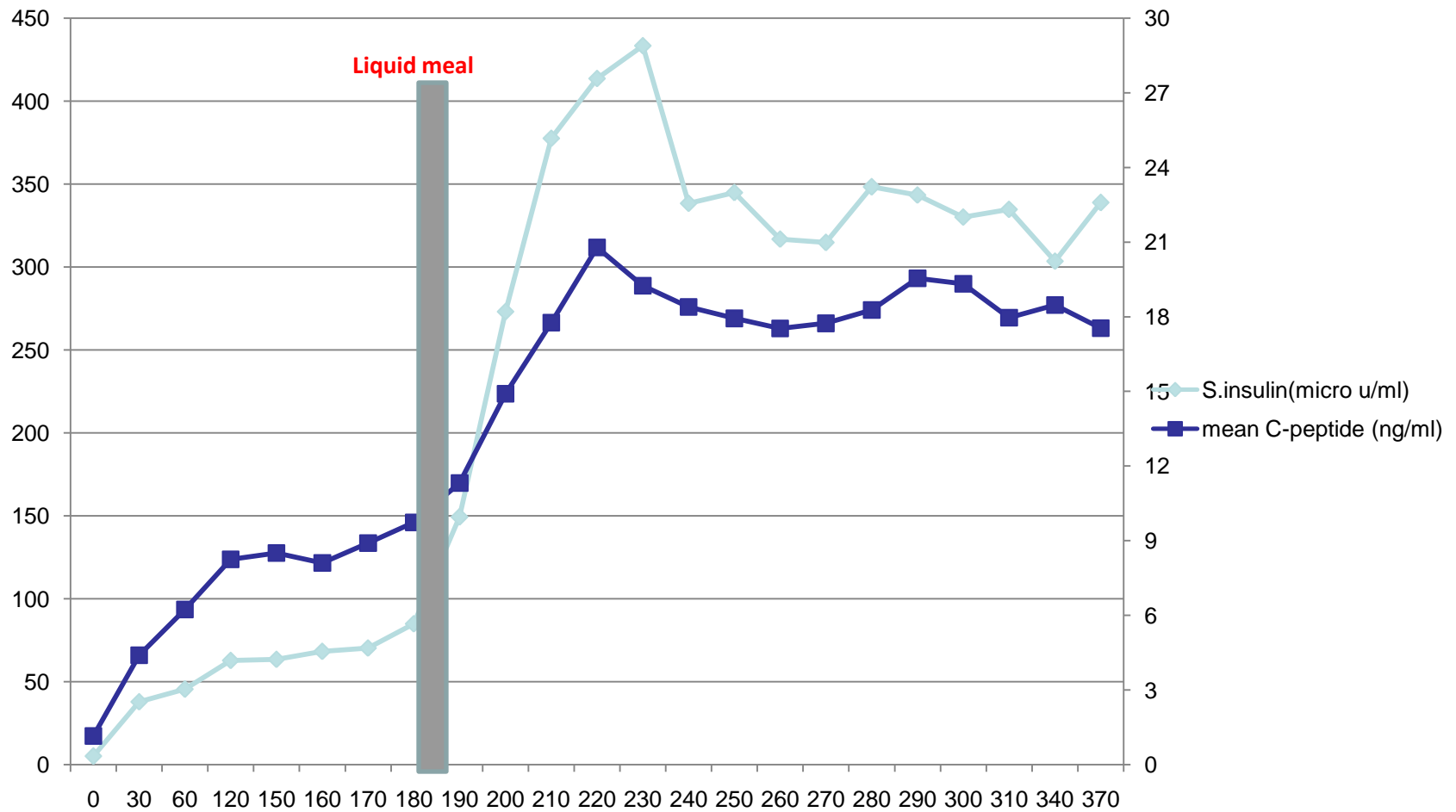
## Summary:

- >90 % of the clamps achieved target B.glucose of 160 ± 5 mg/dl after priming infusion.
- CV% of B.glucose during steady state and post meal state was less than 10% in majority of cases indicating competent quality of clamp to analyze PD results

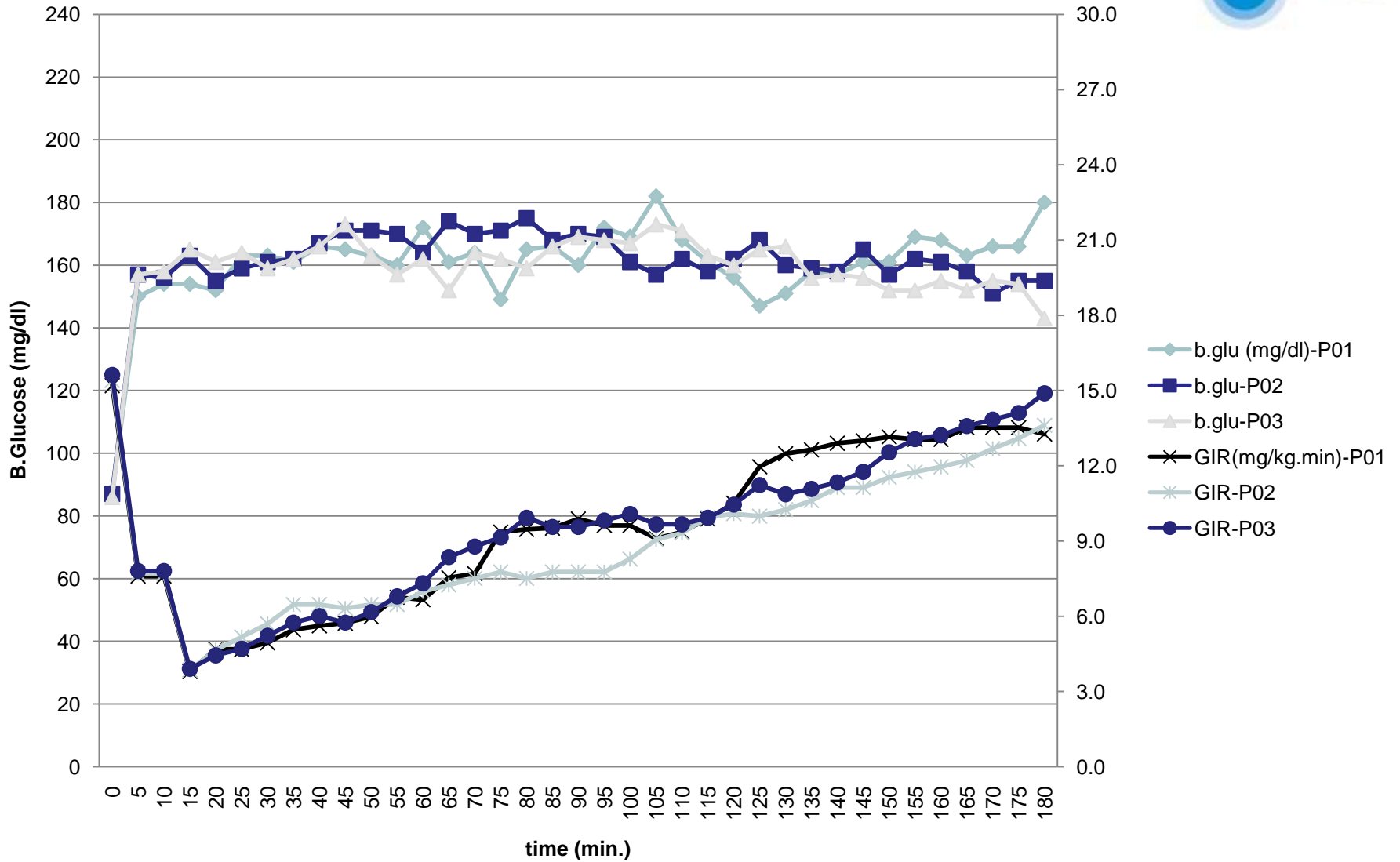
# *B.glucose and GIR Graph*



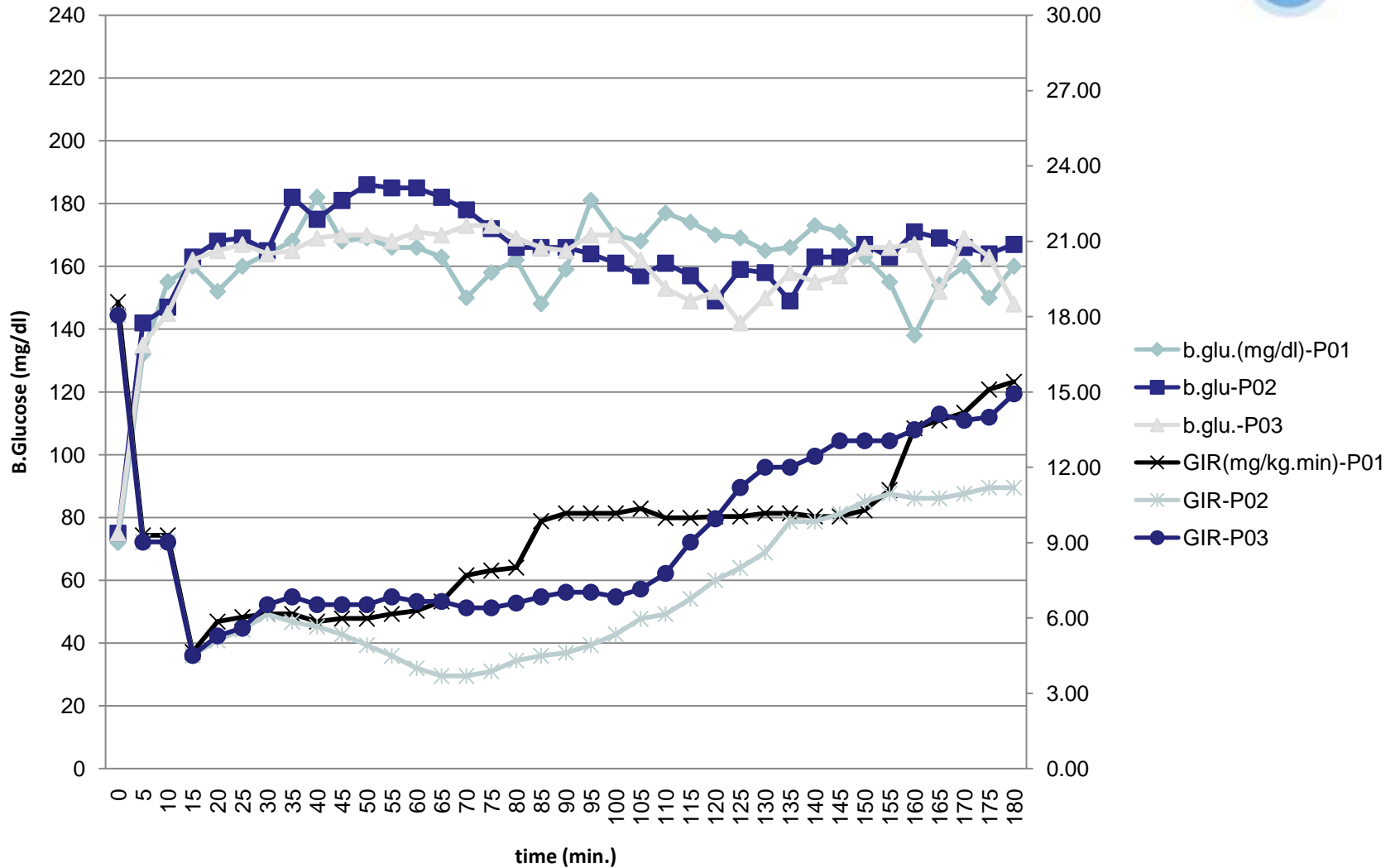
# Insulin and C-peptide Graph



# Subject A



# Subject B





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