Modelling Insulin Clearance and Degradation in Very Premature Infants

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MŰEGYETEM 1782

Motivation

Hyperglycemia is a common complication in ELBW and VLBW infants due to:

- Prematurity
- Infection
- Stress

Incidence

- Increases with lower birth weight [1]
- Increases with over feeding [2]
- Depends on threshold used

Thresholds in literature:

6.9 mmol/L: 43-100% [3-5]
8.0- 8.3 mmol/L: 30-70% incidence [1,6-8]
16.7 mmol/L: 72% [3]

[1] Louik et al, 1985
[2] Cowett et al, 1979
[3] Dweck and Cassady, 1974
[4] Brans et al, 1974
[5] Zarif et al, 1976
[6] Heimann et al, 1974
[7] Hays et al, 2006
[8] Hall et al, 2004

Motivation

Hyperglycaemia has been associated with adverse outcomes in this cohort

- **Greater mortality**
- **Greater morbidity**
  - Increased risk of infection
  - Increased Intraventricular haemorrhage
  - Increased ventilator dependence
  - Increased length of hospital stay
  - Retinopathy of prematurity

On the other hand, **Hypoglycaemia has been associated with adverse neurodevelopmental outcomes**

Tight Glucose Control

Hypoglycaemia

Motivation

No widely accepted treatment method or protocol to treat hyperglycaemia

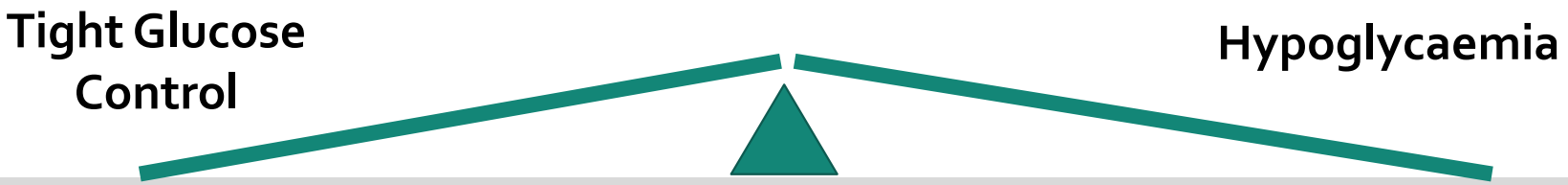
- Often ad hoc or fixed (not patient specific)
- No consensus on target range or thresholds for intervention [1]

→ Glucose restriction

- Lower risk of hypoglycaemia than insulin therapy
- Reduced glucose intake – restricting growth and development

→ Insulin therapy

- Increased glucose tolerance – faster weight gain
- Can reduce blood glucose to “normal” levels
- Increased risk of hypoglycaemia



Glycaemic Control

Model-based glycaemic control for intensive care patients

→ Model based: use mathematics to describe and predict glucose and insulin response to therapy

→ Glycaemic control: Targeting a blood glucose range of 4-8 mmol/L

→ Quantify and manage the risk of hypoglycaemia

Aim: Balance the risks and benefits of tight glycaemic control

Tight Glucose Control

Hypoglycaemia

Model-Based Glycaemic Control

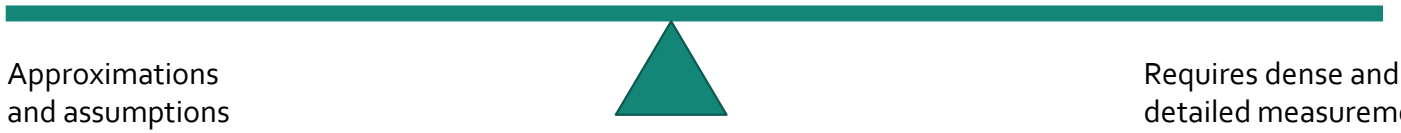
Effective Model-Based Glycaemic Control must:

Have a good model

- Sufficiently describing key physiology, mechanisms, and pathways
- Mathematically identifiable using common clinical measures

Clinically identifiable and useful

Physiologically accurate



Approximations and assumptions

Requires dense and detailed measurements

Aim of this study

To model insulin kinetics in premature infants

Specifically looking at clearance of insulin via:

- Kidney
- Liver
- Cellular degradation
- Diffusion between compartments

Challenge!

The typical blood volume of a very premature infant is approximately 50 mL/kg – roughly the volume of a shot glass

So in premature infants we cannot

-Take serial measurements

-Do invasive measurements

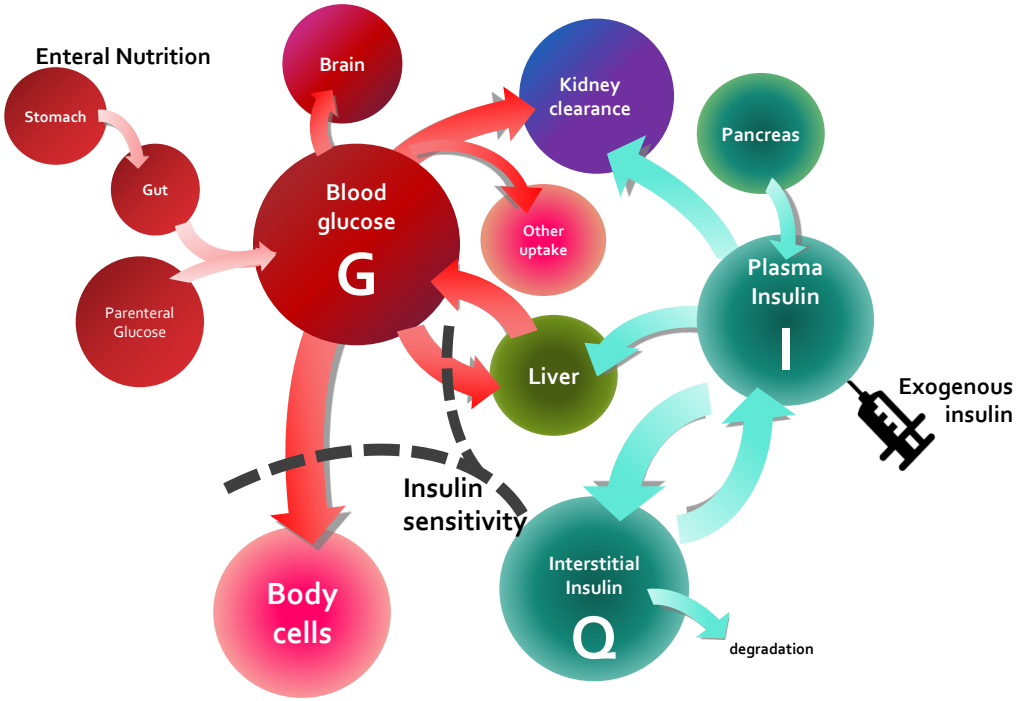
Methods

Therefore, this study is going to use:

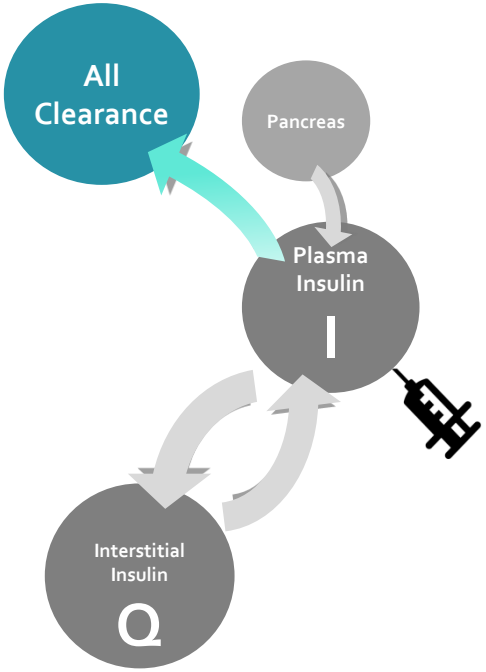
- A unique set of one off blood samples from premature infants analysed for: glucose, insulin, C-peptide, IGF-I
- Data from the literature
- Approach of Pielmeier et al., 2010

Model

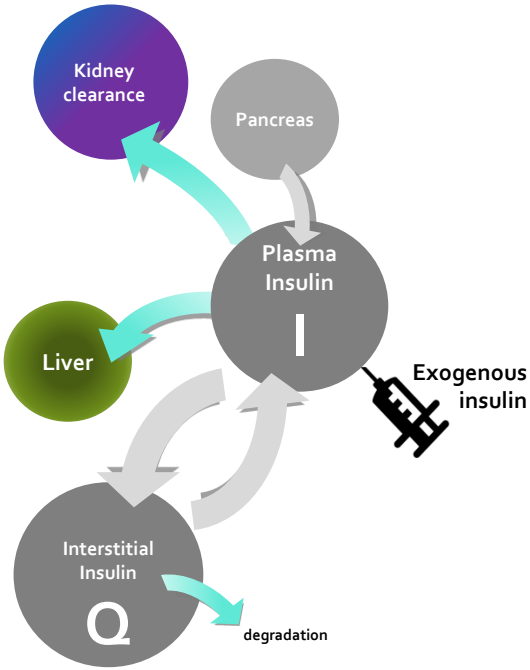
- Based off an existing model of adult glucose-insulin physiology (ICING model)
  - In turn based off minimal model
- Adapted for known differences in neonatal physiology



More descriptive model of insulin



Old model



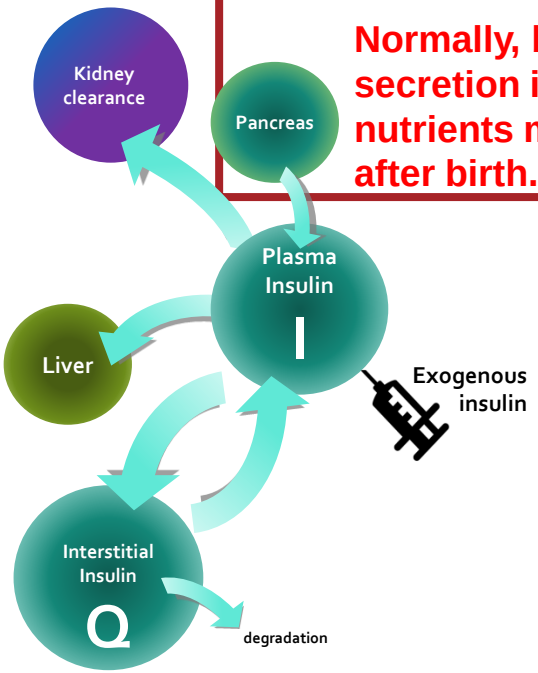
New model

Glucose-insulin kinetic model

Using mathematics to describe physiological changes in insulin and glucose

Mature insulin secretion is a bi-phasic secretion of insulin from the pancreas in response to nutrients and elevated BG

Normally, bi-phasic insulin secretion in response to nutrients may not mature until after birth.



Glucose-insulin kinetic model

Using mathematics to describe physiological changes in insulin and glucose

About 50% of circulating insulin is cleared by the kidneys via glomerular filtration and absorption from the peritubular capillaries

Kidney function increases with GA. Premature infants have higher plasma insulin concentrations, possibly due to reduced clearance

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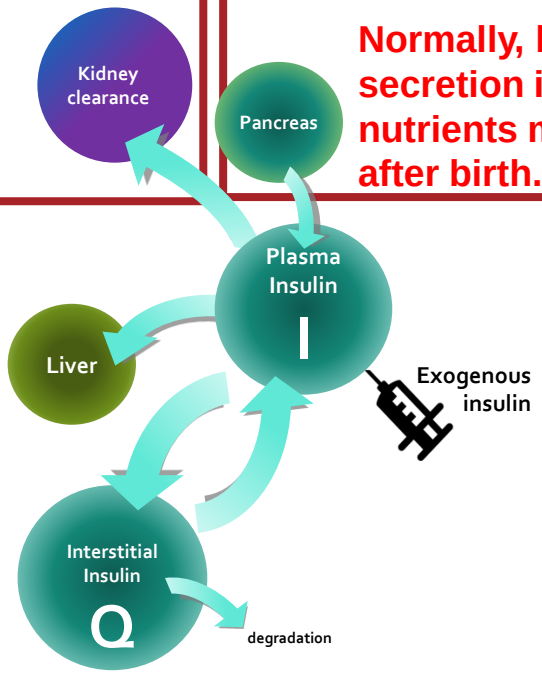

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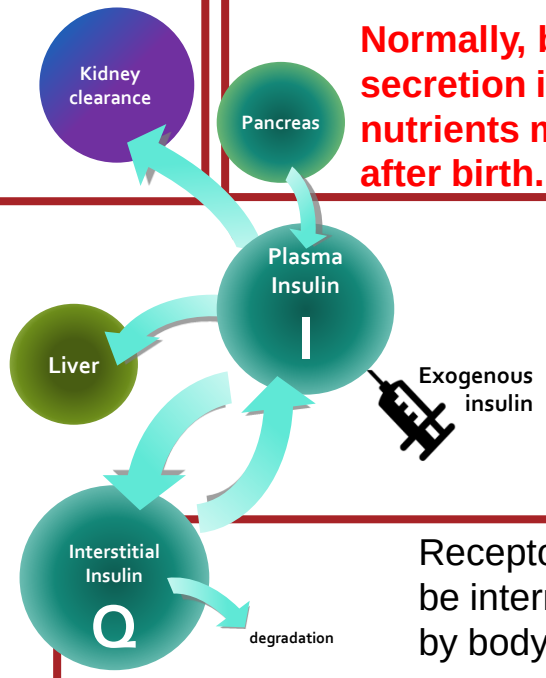

Receptor bound insulin can be internalised and degraded by body cells

Insulin binding to receptors is a saturated process in adults, but has not been observed to be in premature infants.

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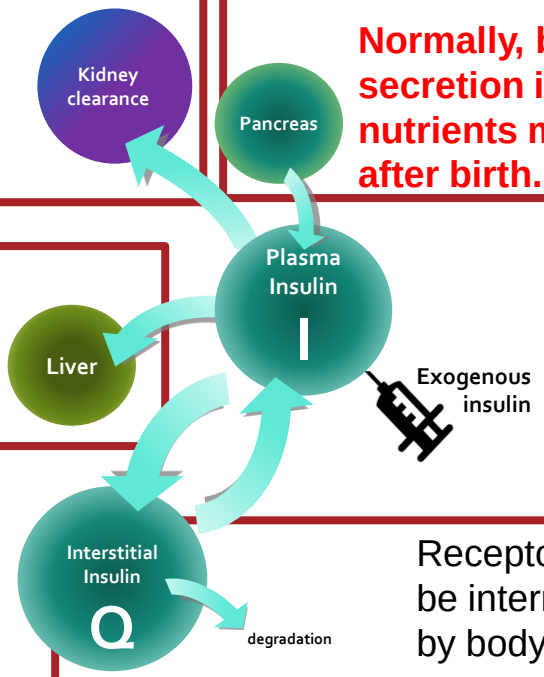
The liver does a first pass clearance of insulin secreted by the pancreas, as well as clearing circulating insulin from the bloodstream.



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The Model – INSULIN

Model describes both peripheral and plasma insulin…..

PERIPHERAL INSULIN

$$\dot{Q} = n_I \frac{V_P}{V_Q}\left(I(t) - Q(t)\right) - n_C \frac{Q(t)}{1 + \alpha_G Q(t)}$$

degradation

Diffusion between plasma and periphery

Exogenous insulin

Pancreatic Insulin Secretion

Pancreas

PLASMA INSULIN

$$\dot{I} = -\frac{n_L I(t)}{1 + \alpha_I I(t)} - n_K I(t) - n_I\left(I(t) - Q(t)\right) + \frac{u_{ex}(t)}{V_P m_{body}} + 1 - x_L\, u_{en}(t) m_{body}$$

Kidney clearance

Kidney

Liver clearance

Liver

First pass hepatic extraction

Clinical data - HINT cohort

Blood samples obtained from a randomised control trial of blood glucose control in very premature infants (HINT trial, Auckland)

→Infants <32 weeks and/or weighing less than 1.5 kg at birth

→Infants randomised when they became hyperglycaemic (2 BG>8.5 mmol/L at least 4 hours apart)

Characteristic	Value
Total patients	41
Control group	21
Tight Glycaemic Control group	20
Male (%)	20 (49%)
Multiple Birth	11 (27%)
Antenatal glucocorticoid exposure	39 (95%)
Maternal diabetes	1 (2%)
Gestational age, weeks	**27.2 [26.2 - 28.7]**
Birth weight (grams)	**839 [735 – 1000]**
Birth weight Z score	-0.19[-1.03 - 0.14]
Small for gestational age	6 (15%)
CRIB 2 score	12 [10-14]
Ethnicity	
Asian	9 (22%)
Caucasian	11 (27%)
Maori	17 (41%)
Pacific Island	4 (10%)

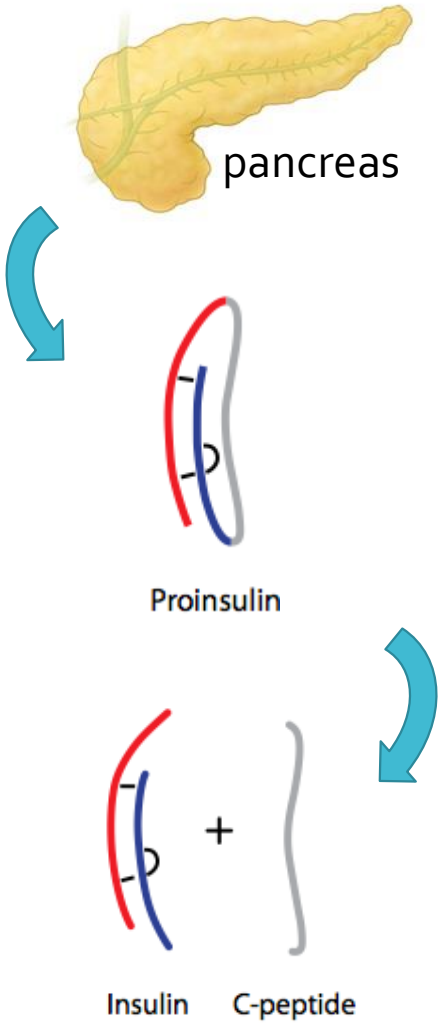
HINT – study protocol for blood sampling

Blood samples taken at randomisation, and 7 and 14 days post randomisation

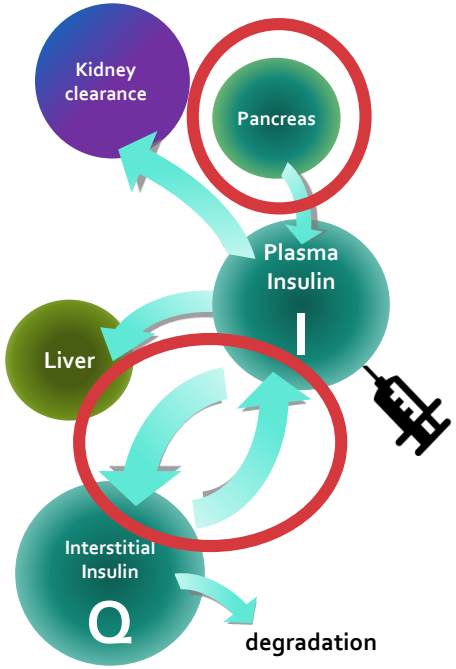
- **Analysed for: Glucose, Insulin, IGF-I, C-peptide**

Smaller, intermittent samples taken ~ 4 – 8 hours daily for blood glucose control

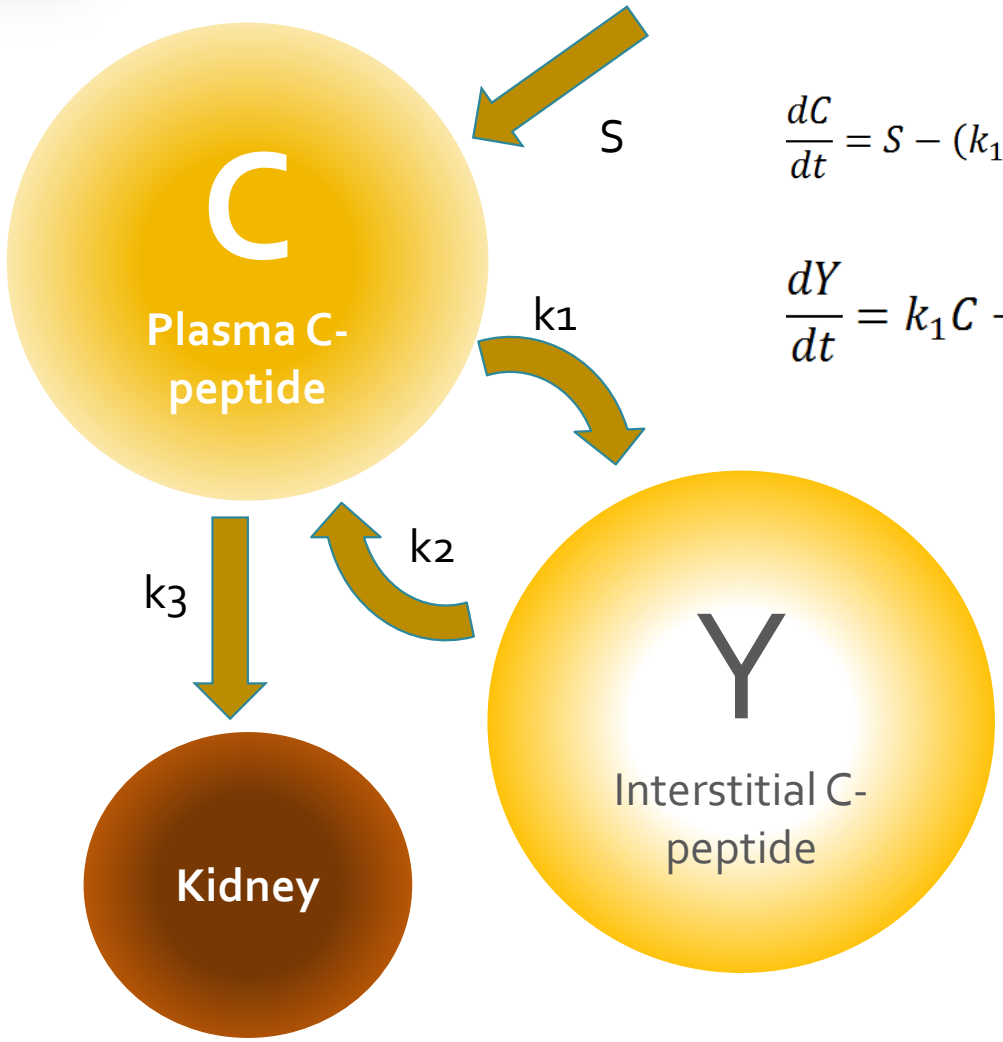
Modeling Insulin Clearances



C-peptide is a molecule secreted in equi-molar quantities to Insulin. We can use its simpler dynamics to estimate insulin secretion and diffusion between compartments

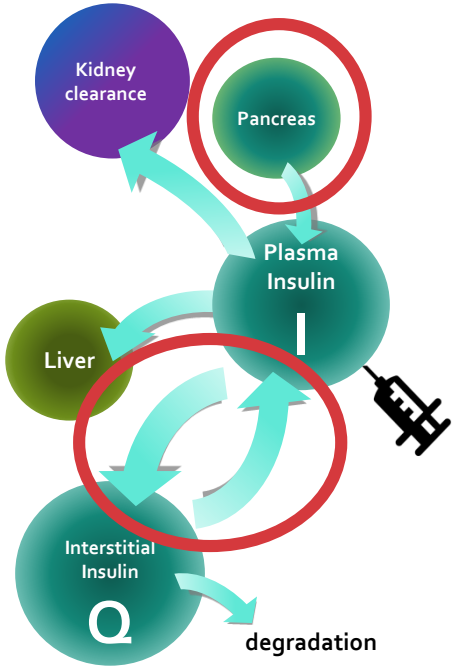


Modeling Insulin Clearances

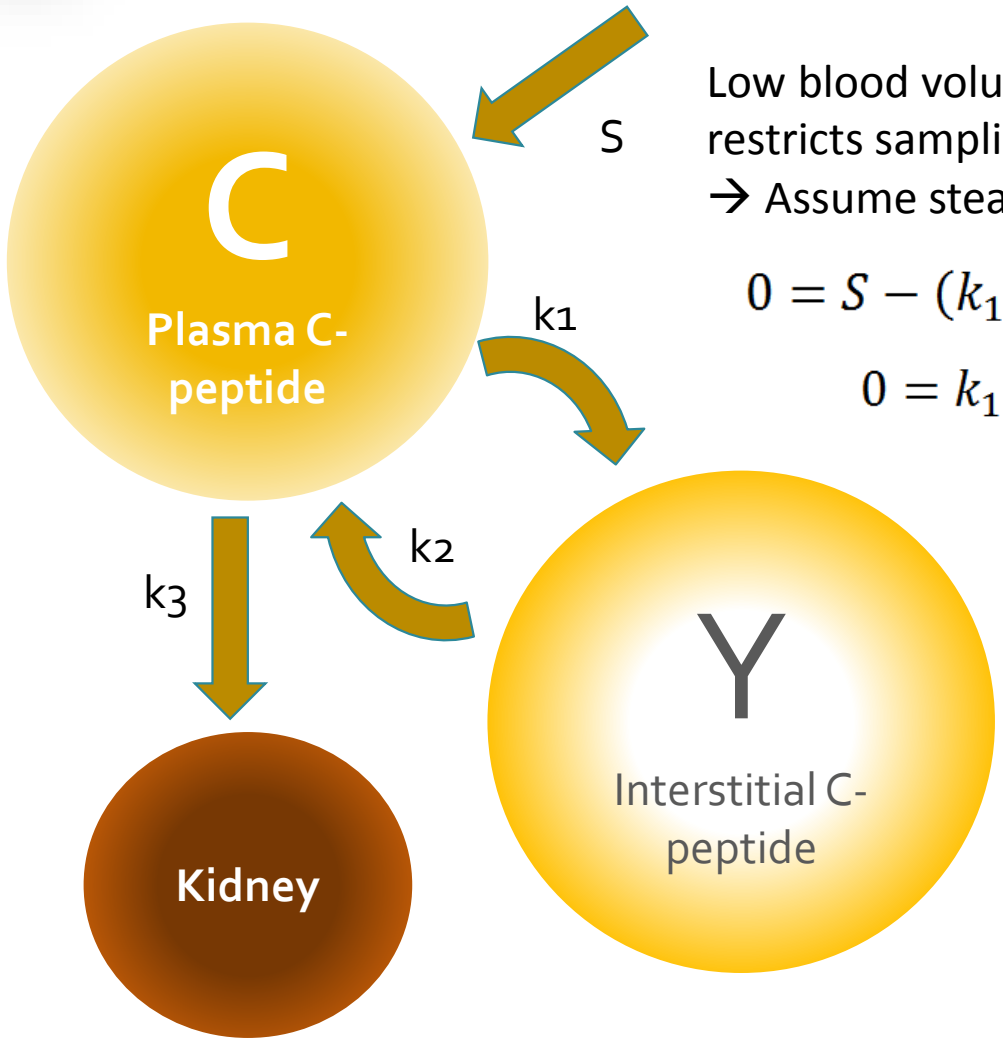


$$\frac{dC}{dt} = S - (k_1 + k_3)C + k_2 Y$$

$$\frac{dY}{dt} = k_1 C - k_2 Y$$



Van Cauter model of C-peptide



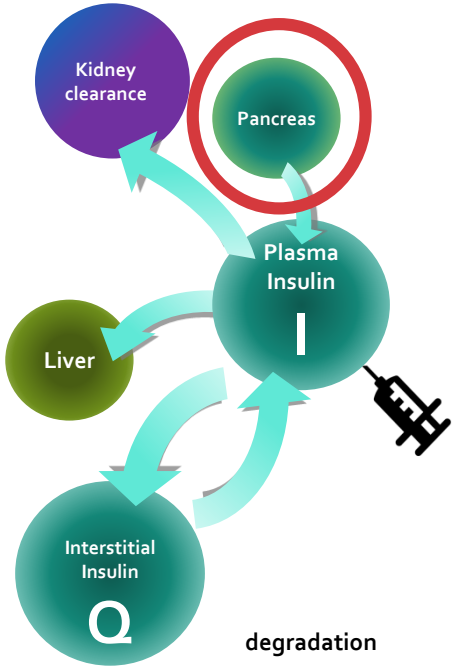
Low blood volume of extremely premature infants restricts sampling.
→ Assume steady state at time of sampling:

$$0 = S - (k_1 + k_3)C + k_2 Y$$

$$0 = k_1 C - k_2 Y$$

$$k_1 C = k_2 Y$$

$$\boxed{S = k_3 C}$$



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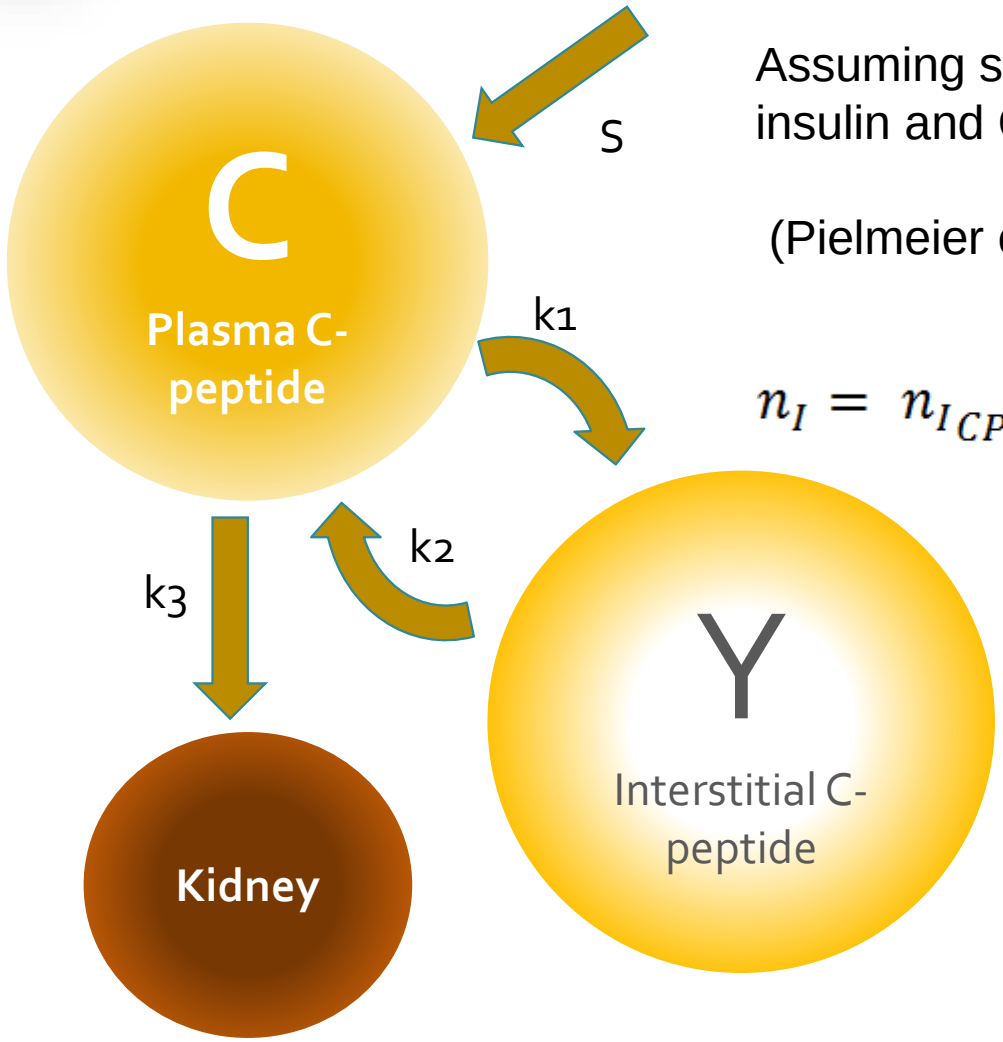
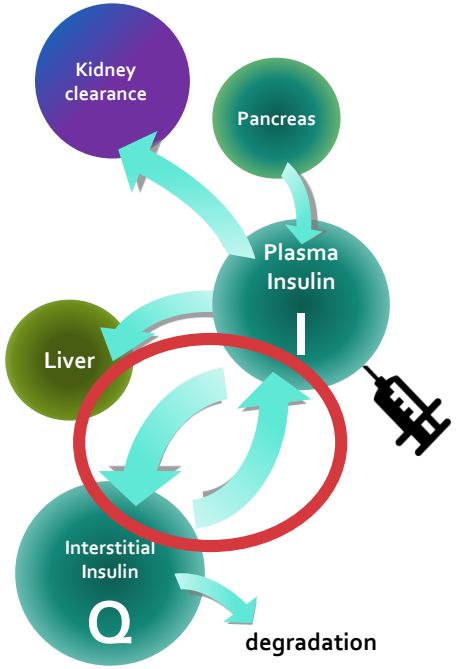


Assuming similar diffusive properties between insulin and C-peptide,

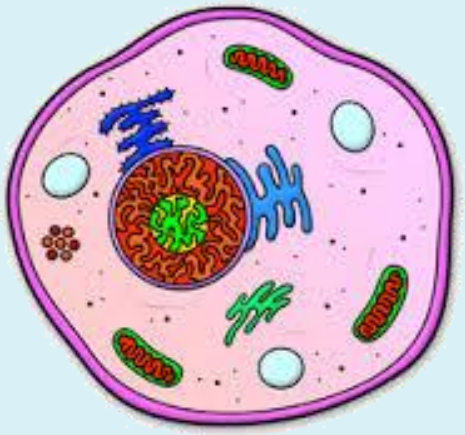
(Pielmeier et al., 2010):

$$n_I = n_{I_{CP}} \frac{m_c}{m_I} = k_1 \frac{m_c}{m_I}$$



Cellular degradation of insulin

Receptor bound insulin can be internalised by a cell



And then degraded

Taking the interstitial insulin equation

$$\dot{Q} = n_I \frac{V_I}{V_Q}\left(I(t) - Q(t)\right) - n_C \frac{Q(t)}{1 + \alpha_G Q(t)}$$

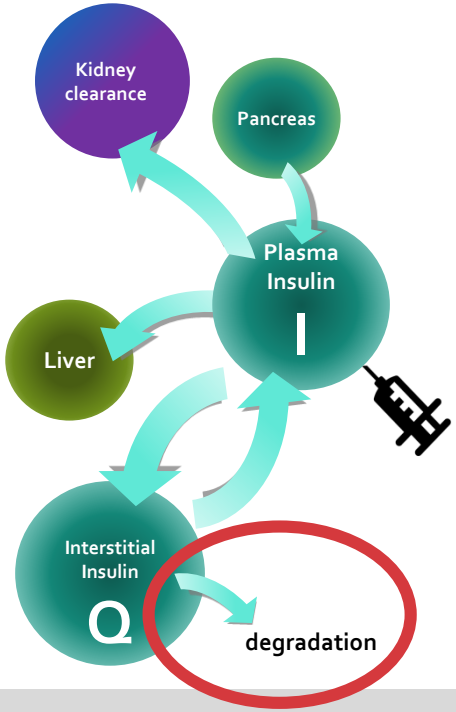
↓

Assume steady state

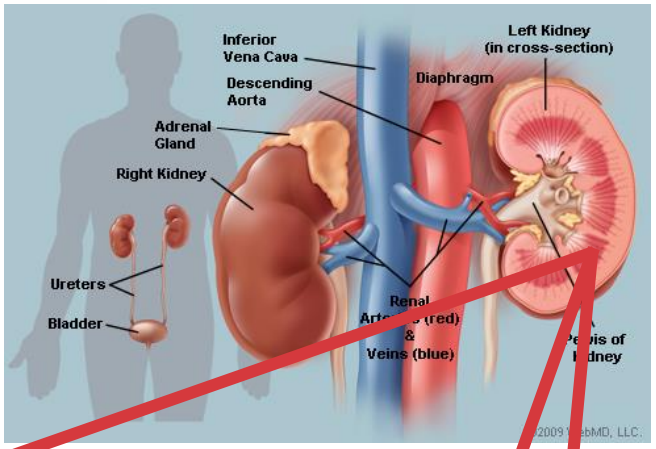
↓

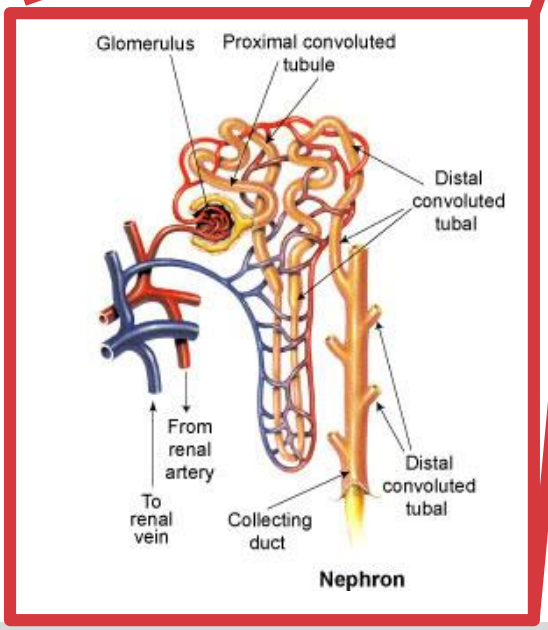
$$n_C = n_I \frac{V_I}{V_Q}\left(\frac{I_{ss}}{Q_{ss}} - 1\right)$$

And, Iss/Qss is approximately 0.5 (Gudbjornsdottir et al., 2003, Sjostrand et al., 1999, 2000, and 2005)



Kidney clearance of insulin



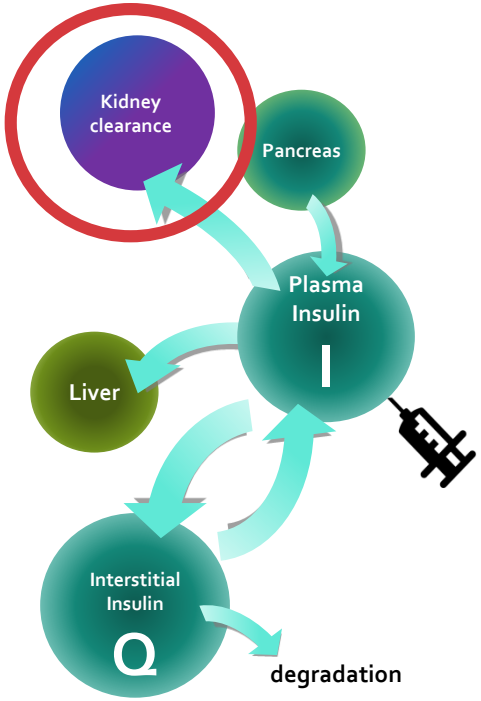


Kidney function in premature infants:

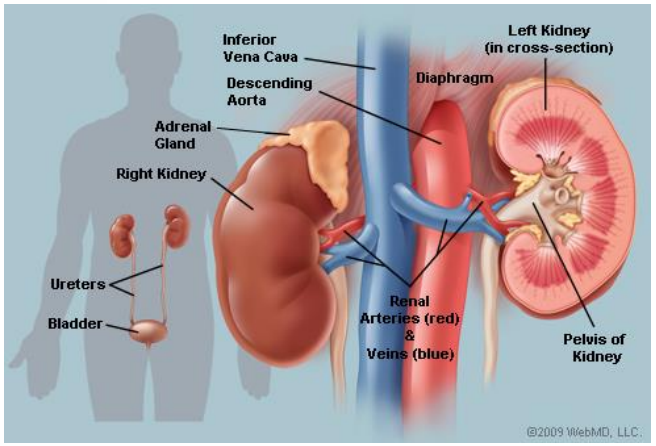
- Insulin is cleared both in glomerular filtration and proximal tubal reabsorption and degradation

- About 60% of total insulin clearance by the kidneys occurs in the glomerulus

$$\text{Total kidney clearance of insulin} = \frac{GFR_{insulin}}{0.6}$$



Kidney clearance of insulin



Kidney function in premature infants

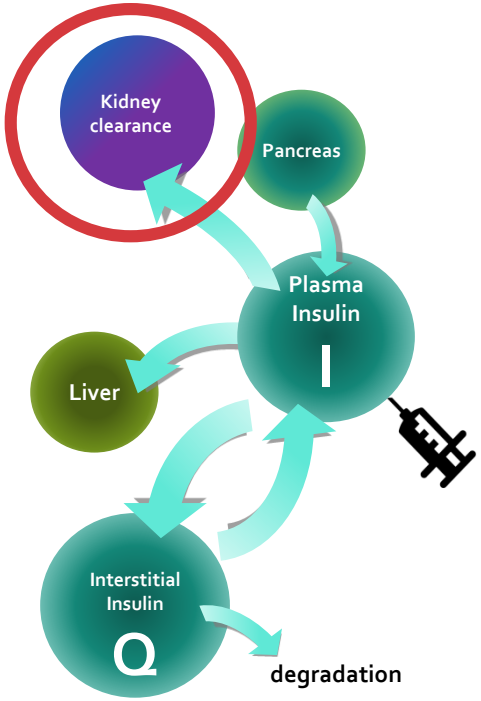
- Two common measures of GFR use creatine and inulin (NOT a typo) as markers

- The rate of GFR for insulin is approximately 90% that of inulin determined GFR (Maack et al., 1979)

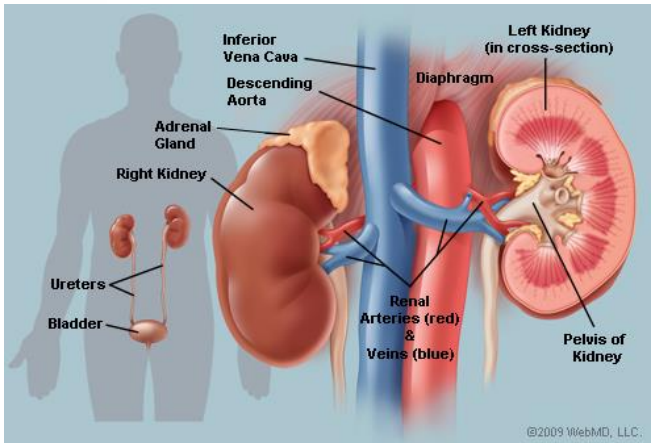
$$\text{Total kidney clearance of insulin} = \frac{0.9\ GFR_{inulin}}{0.6}$$

Thus, the clearance constant is

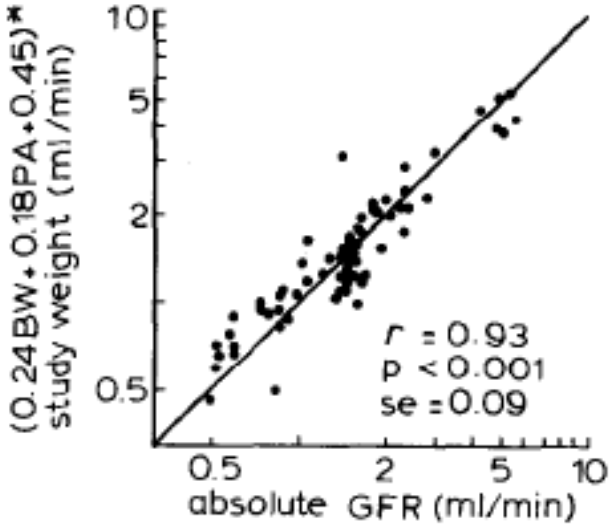
$$n_K = \frac{1}{V_p} \times \frac{0.9\ GFR_{inulin}}{0.6}$$



Kidney clearance of insulin



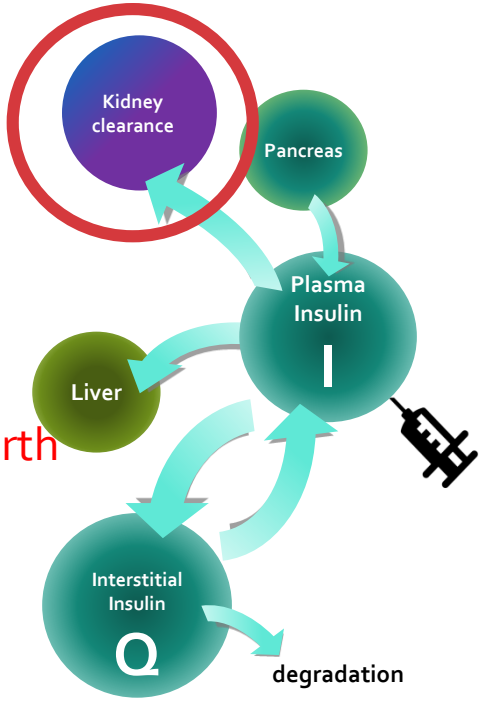
Inulin based GFR behaviour has been studied (Coulthard, 1985)



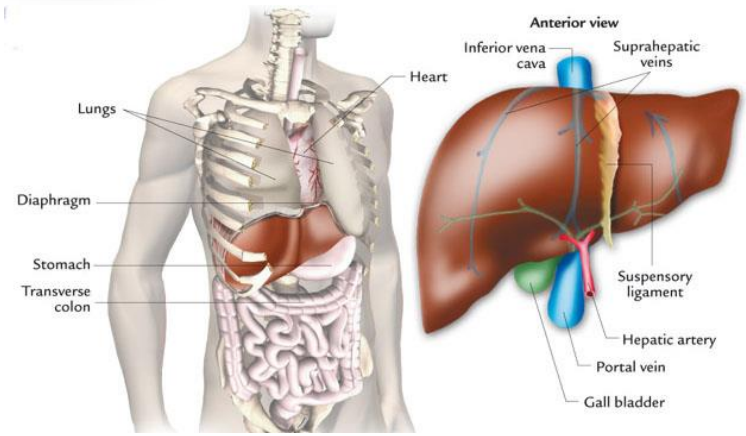
Birth weight

$$GFR = 0.45 + 0.24m_{bw} + 0.18A_{pN}$$

Days since birth



Liver clearance of insulin



Liver clearance involves:

- A first pass clearance of insulin secreted into the portal vein by the pancreas
  → not identifiable here, estimated from the adult value (Lin et al, 2011)

$$x_L = 0.67$$

- Clearance of circulating insulin in blood

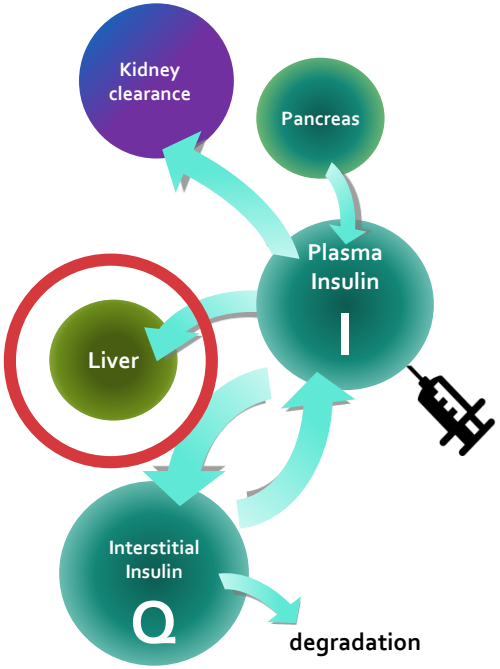
$$\dot{I} = -\frac{n_L I(t)}{1+\alpha_I I(t)} - n_K I(t) - n_I\big(I(t) - Q(t)\big) + \frac{u_{ex}(t)}{V_p\, m_{body}} + (1-x_L)u_{en}(t)\, m_{body}$$

↓

Assume steady state

↓

$$n_K + n_L \approx \frac{-n_I(I_{ss} - Q_{ss}) + \frac{u_{ex}(t)}{V_p} + (1-x_L)u_{en}}{I_{ss}}$$



Results

HINT Cohort: Parameter results

Parameter	Preterm infant value [1/min]	Adult ICING model value [1/min]	Adult range Median [Range] (Lotz et al., 2008) [1/min]
n_I	0.025	0.003	0.28 [0.22-0.36] **[L/min]** 0.0052 [0.0041 – 0.0119] **[1/min]***
n_K	0.021 [0.020-0.22]	0.054	0.15 [0.1-0.21]
n_L	0.39 [0.15-0.70]	0.158	0.06 [0.064-0.53]
$n_c \frac{V_Q}{V_P} = n_I \left(\frac{I_{ss}}{Q_{ss}} - 1\right)$	0.025	$n_c = n_I$	-

*From Pretty et al. (2014)

Diffusion between plasma and interstitial fluid faster than adult ICING model

Results

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Kidney clearance is patient specific based on weight and post natal age. Values similar to adult range.

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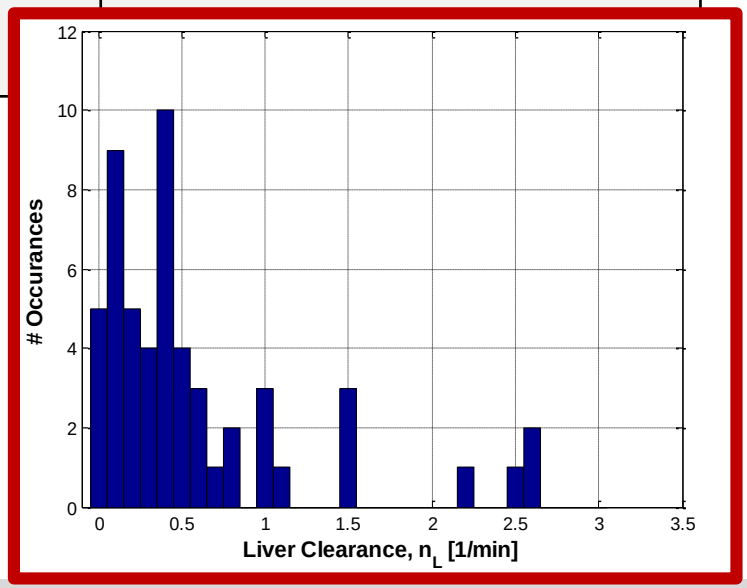

Liver clearance highly variable, which may also reflect patient specific deviations from other modelled clearance values

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*From Pretty et al. (2014)

Cellular degradation dependant on diffusion into interstitial compartment, and is scaled by fluid volumes of distribution.

→ (previous work has shown interstitial fluid volume to contract in first week of life, which is currently modelled)

Clinical data validation

To check model performance, the model is fit to clinical data from two neonatal cohorts

→ Christchurch Women's Hospital (CWH)

→ Auckland HINT trial cohort

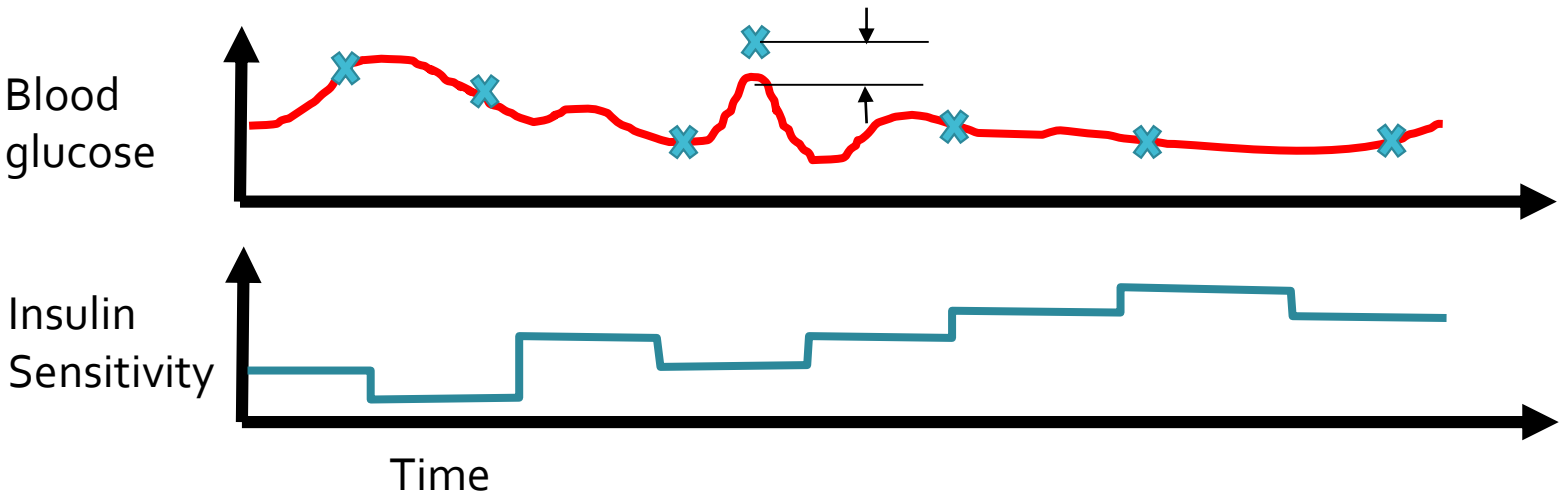
Both cohorts: blood glucose (average time between measures: 4 hours), insulin and nutrition data recorded.

	HINT	CCH
Total Number	55	62
Male/female	27/28	29/33
Gestational age, wks	25 [24–26]	27 [25–28]
Post natal age, days	4 [3–8]	2 [0–5]
Weight, grams	690 [740–890]	865 [690-960]
Total BG measures	1389	2951
Measurement interval, hours	4.0 [3.5–4.8]	3.3 [2.8–3.9]
Median BG, mmol/L	7.10 [4.90–9.40]	7.10 [5.70–9.00]
Median insulin rate, U/kg/hr	0.06 [0.04–0.08]	0.04 [0.03–0.05]

Clinical data validation

Two errors considered:

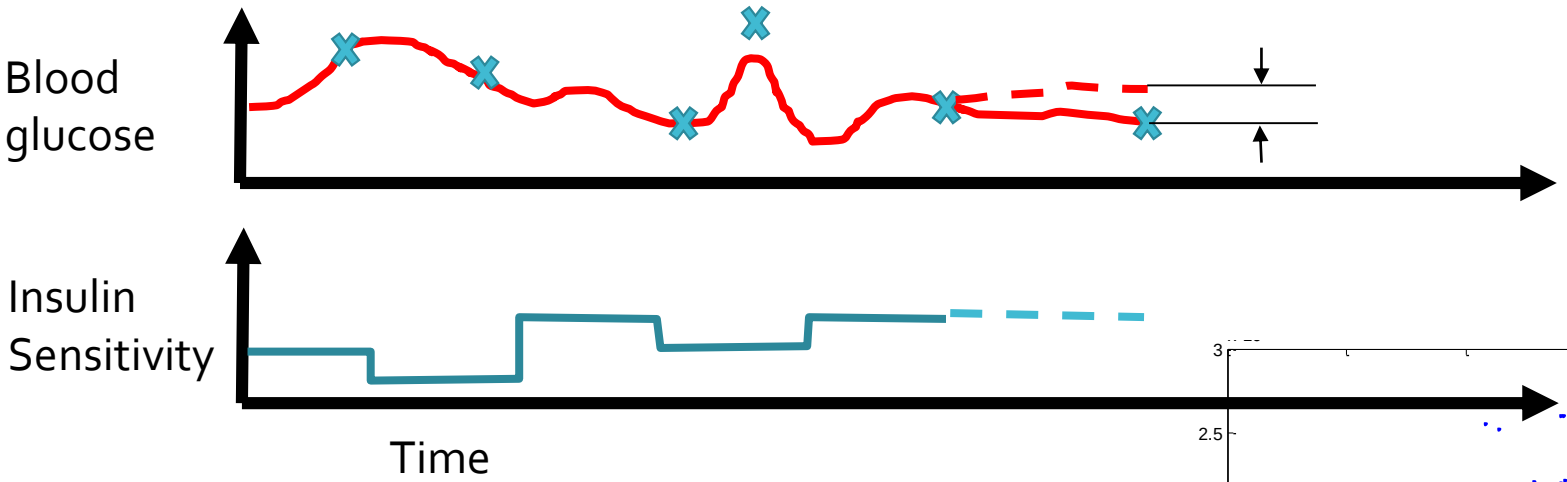
→Fitting error: % difference between measured and modelled blood glucose

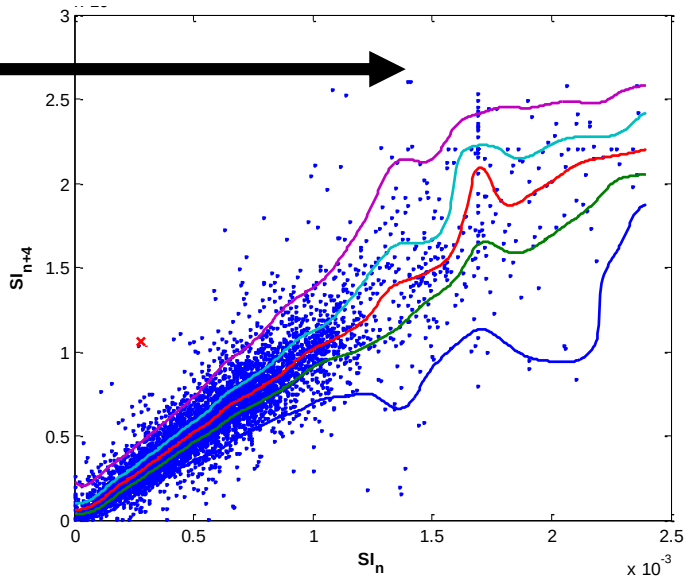


Clinical data validation

Two errors considered:

→Prediction error: Accuracy of mean likely prediction outcome





Clinical data validation

Model fit

	CWH Cohort	HINT Cohort
New model		
Fitting Error	2.1%	2.7%
Prediction Error	12.6 [5.2-24.7] %	18.3 [7.3-34.0] %
Old model		
Fitting Error	2.1%	2.9%
Prediction Error	11.7 [5.1-23.5] %	18.8 [8.1-37.0] %

→ **Similar fitting and prediction error between these two models**

→ **Recent clinical results with new model and new protocol has shown improvement over previous model and protocol**

- → **7% more BG in target range (70 → 77%)**
- → **Less hypoglycaemia (3.5 → 0.5 % BG below 4.0 mmol/L)**

Conclusions

- Updated modelled insulin kinetics for model-based glycaemic control in neonatal intensive care
- Use of clinical data and literature results
- More physiologically descriptive
- Greater tailoring of some clearance parameters to patient age and/or weight
- Similar model fitting, but improved clinical results with new model

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Any Questions?