Determining the effects of insulin Detemir on endogenous secretion of insulin

Jacob B. Klenner, Benjamin A. Van Noorden, Jennifer L. Knopp, Lui R. Holder Pearson, Anna R. Hardy, Sarah L. Vergeer, Geoffrey M. Shaw, J. Geoffrey Chase

***Abstract*— *Abstract*— Type 2 diabetes (T2D) is a long-term metabolic disorder. A pilot trial was designed to investigate the effects of the long acting insulin Detemir on endogenous insulin secretion, to assess use in early T2D care. Provesn metabolic system models are used to identify patient-specific insulin sensitivity and endogenous insulin secretion from clinical data. Post-cardiac surgery patients with early T2D or pre-diabetes based on HbA1c were given a bolus of insulin Detemir on one day, and none on the second day in hospital. Blood glucose, insulin, C-Peptide, and all nutrition given are recorded. Early results from N=3 patients show 0.8-1.0U/hour insulin Detemir doses have no apparent suppression of endogenous insulin secretion, but does help lower glucose levels. The results show the model captures glucose-insulin dynamics in pre-diabetic post-surgical patients, and insulin Detemir may be useful to support individuals with pre-diabetes in reducing blood glucose levels. Tests with higher doses, need to be carried out to verify these results over a greater range of patients.**

I. Introduction

Type 2 diabetes (T2D) is a long-term metabolic disorder characterised by insulin resistance, hyperglycaemia, and reduced endogenous insulin secretion. The overall prevalence of T2D of approximately 366 million in 2011 is expected to rise to 552 million by 2030 [1], with significant costs of ~1% GDP rising to 1.5% or more by 2030. Its scale and cost is a dominant factor in the growing need to find ways to delay the incidence and increasingly costly progression of T2D.

Insulin Detemir is a long-acting insulin designed to provide a basal plasma insulin rate, modified by an added long-chain fatty acid which binds to albumin in plasma, existing in rapid equilibrium in bound and unbound states with ~2-4 % unbound at any time [2, 3]. Only in the unbound state is insulin Detemir free to facilitate cellular glucose uptake. The appearance and bio-availability of Insulin Detemir has not been previously modelled.

The ORIGIN study [4] investigated the effects of long acting insulin glargine and insulin therapy on a range of health outcomes. A key result was the use of insulin, even with low compliance, reduced the incidence of progression from pre-diabetes

to T2D. Given even a single year delay in incidence can have significant overall cost and quality of life outcomes [5], this result indicates a potential role for early insulin use as basal support in pre-diabetes. In contrast, insulin therapy is currently a "last resort" drug in T2D for safety reasons [6].

This study presents an analysis of pilot results from a trial using Detemir in pre-diabetic patients. The trial goal is to assess the impact of Detemir as a basal analogue to support (without suppressing) pancreatic, as a first step in studying early use of long acting insulin to delay progression from pre-diabetes to T2D. This analysis uses model-based methods to model the appearance of bio-available Detemir, and assess its effect on insulin secretin.

II. MODELLING

Mathematical compartment models incorporating patient glucose-insulin data and enabling endogenous insulin production estimation are adapted from previous work [7, 8].

A. Gastrointestinal Model

Glucose appearance following meal ingestion is described by a gastrointestinal model [9], describing solid (q_{sto1}, mmol) and liquid (q_{sto2}, mmol) glucose content of a meal in the stomach, and the glucose in the intestines (q_{gut}, mmol):

$$\dot{q}_{sto1} = D(t) - k_{21} \cdot q_{sto1} \quad (1)$$

$$\dot{q}_{sto2} = k_{21} \cdot q_{sto1} - k_{empt}(q_{sto}) \cdot q_{sto2} \quad (2)$$

$$\dot{q}_{gut} = k_{empt}(q_{sto}) \cdot q_{sto2} - k_{abs} \cdot q_{gut} \quad (3)$$

The rate of glucose appearance in blood plasma, (R_a) is:

$$R_a = f \cdot k_{abs} \cdot q_{gut} \quad (4)$$

In Equations 1-4, $D(t)$ is the rate of delivery of glucose or carbohydrates into the stomach, estimated by dividing meal size by duration. Note, $f \leq 1$ is a scaling factor for incomplete absorption and first-pass hepatic clearance.

The stomach emptying rate, $k_{empt}\,(min^{-1})$, is a function of the size of the meal remaining in the stomach relative to the total meal size, D_{tot}, and defined:

$$k_{empt} = k_{min} + \frac{k_{max} - k_{min}}{2}.\alpha$$

$$\alpha = \tanh[\alpha(q_{sto} - b \cdot D_{tot})] - \tanh[\beta(q_{sto} - c \cdot D_{tot}] + 2 \quad (5)$$

$$q_{sto} = q_{sto1} + q_{sto2} \quad (5)$$

$$\alpha = \frac{5}{2 \cdot D_{tot} \cdot (1-b)} \quad (6)$$

$$\beta = \frac{5}{2 \cdot D_{tot} \cdot c} \quad (7)$$

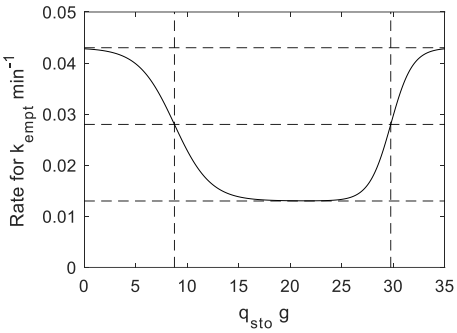


Figure 1. Depiction of k_{empt} as a function of q_{sto} for a 35 g carbohydrate meal. Horizontal dashed lines from top-bottom indicate the maximum, mean and minimum emptying rates.

$D_{tot} = 10^{-3}$ is used during fasting to avoid singularity. Figure 1 describes the dynamics of Equation 5 as stomach glucose quantities change over time for 35g carbohydrate. Further parameter values and definitions are found in Table 1.

B. Glucose-Insulin Modelling

Blood glucose, *G* (mmol/L), and plasma, *I* (mU/L), and interstitial insulin, *Q* (mU/L), dynamics are modelled [7]:

$$\dot{G} = -p_g(G - G_{fast}) - S_I \frac{G(Q + Q_{DF})}{1 + \alpha_G(Q + Q_{DF})} + \frac{R_a + EGP - CNS}{V_G} \quad (9)$$

$$\dot{I} = -n_K \cdot I - n_L \frac{I}{1 + \alpha_I I} - n_I(I - Q) + U_{en} \frac{(1 - x_L)}{V_I} \quad (10)$$

$$\dot{Q} = n_I(I - Q) - n_c \frac{Q}{1 + \alpha_G \cdot Q} \quad (11)$$

Insulin sensitivity (S_I) and fasting blood glucose (G_{fast}) are time dependant. G_{fast} for each day was the first glucose measurement prior to breakfast. S_I is a time varying parameter is identified from data. U_{en} is pancreatic secretion rate, estimated from C-peptide measurements [10] and Q_{DF} represents additional insulin from the Detemir analogue,. All other parameter values are detailed in Table 1.

C. Insulin Detemir Model

A seven-compartment model is used for Detemir kinetics, where injected Detemir is hexameric (I_{DH}, mU), and dissociates into dimeric and monomeric insulin:

$$\dot{I}_{DH} = -k_a \cdot I_{DH} + I_{bolus} \quad (12)$$

$$\dot{Q}_{DF,local} = k_a I_{DH} - Q_{DF,local}(k_b + k_{di}) - (k_{d1} \cdot Q_{DF,local} - k_{d2} \cdot Q_{DB,local}) \quad (13)$$

$$\dot{Q}_{DB,local} = k_{d1} \cdot Q_{DF,local} - k_{d2} \cdot Q_{DB,local} \quad (14)$$

Where I_{bolus} (mU) is the subcutaneously injected insulin. Free and albumin bound insulin in the local depot are $Q_{DF,local}$ (mU) and $Q_{DB,local}$ (mU), k_{d1} and k_{d2} are rate constants defining binding and unbinding to albumin. The values for k_{d1} and k_{d2} ensure 4% unbound Detemir at steady state [11]. Further parameter values, units, and definitions are in Table 1.

The model uses four compartments to describe free and bound Detemir insulin in both blood plasma and the whole body interstitial fluid compartment.

TABLE I: PARAMETER VALUES AND UNITS

Parameter		**Value**	**Unit**	**Ref**
Gastrointestinal Model				
$\boldsymbol{k_{21}}$	Stomach grinding	0.054	min^{-1}	[9]
$\boldsymbol{k_{abs}}$	Gut adsorption of glucose	0.071	min^{-1}	[9]
$\boldsymbol{b}$	Parameters describing stomach emptying. See text for details.	0.69	–	[9]
$\boldsymbol{c}$		0.17	–	[9]
$\boldsymbol{k_{max}}$		0.054	min^{-1}	[9]
$\boldsymbol{k_{min}}$		0.006	min^{-1}	[9]
$\boldsymbol{f}$	Scaling factor	0.8	–	[9]
Insulin Detemir Model				
$\boldsymbol{k_a}$	hexameric dissociation into dimers and monomers	0.0078	min^{-1}	[12]
$\boldsymbol{k_{d1}}$	rate constants defining the binding and unbinding of the insulin to albumin	0.96	min^{-1}	[12]
$\boldsymbol{k_{d2}}$		0.04	min^{-1}	[12]
$\boldsymbol{k_{di}}$	degradation of Detemir in the local interstitium	0.0594	min^{-1}	[12]
$\boldsymbol{k_b}$	diffusion of unbound insulin from local depot to blood	0.0181	min^{-1}	[12]
$\boldsymbol{n_K}$	renal clearance of Detemir	0	min^{-1}	[12]
$\boldsymbol{n_{DL}}$ *	Detemir liver clearance	0.288	min^{-1}	[12]
$\boldsymbol{n_{DI}}$	Detemir trans-endothelial	0.06	min^{-1}	[12]

* this is the sum of renal and hepatic clearance rates

** these constants are physiologically identical and are 0.5x the displayed value due to cardiac surgery patients having reduced kidney clearance

$I_{DF}$is the unbound insulin in blood plasma, I_{DB} the bound insulin in plasma, Q_{DF} is unbound insulin in interstitial fluid. and Q_{DB} is the bound insulin in the interstitial fluid, yielding:

$$\dot{I}_{DF} = \frac{k_b}{V_I} Q_{DF,local} - I_{DF}(n_{DL} + n_K) - n_{DI}(I_{DF} - Q_{DF}) - (k_1 \cdot I_{DF} - k_2 \cdot I_{DB}) \quad (15)$$

$$\dot{I}_{DB} = k_1 \cdot I_{DF} - k_2 \cdot I_{DB} \quad (16)$$

$$\dot{Q}_{DF} = -n_{DC} \cdot Q_{DF} + n_{DI}(I_{DF} - Q_{DF}) - (k_1 \cdot Q_{DF} - k_2 \cdot Q_{DB}) \quad (17)$$

$$\dot{Q}_{DB} = k_{d1} \cdot Q_{DF} - k_{d2} \cdot Q_{DB} \quad (18)$$

Further details are in Table 1.

D. Endogenous Insulin Secretion

C-peptide is secreted in equimolar quantities with insulin, but only cleared by the kidney, providing a convenient means to estimate endogenous insulin secretion using a model describing plasma $(C, pmol/L)$ and peripheral $(Y, pmol/L)$ C-peptide concentrations [10]:

$$\dot{C} = U_{en} - C(k_1 + k_3) + k_2 \cdot Y \quad (8)$$

$$\dot{Y} = k_1 \cdot C - k_2 \cdot Y \quad (9)$$

Further details are in Table 1. Eqs 19-20 can be solved for U_{en}:

$$U_{en} = -k_1 C(t_0) \cdot \exp[-k_2(t - t_0)] + \mathrm{k_1 k_2} \int_{t_0}^{t} C(s) \cdot \exp[-k_2(t - s)]\, ds + \dot{C} + C(k_1 + k_3) \quad (10)$$

Endogenous secretion, U_{en}, can then be input to Equation 10.

	diffusion			
n_{DC}	Detemir: peripheral degradation	0.032	min^{-1}	[12]
Glycaemic Control Model				
p_g	the non-insulin mediated uptake	0.06	min^{-1}	[8]
SI	Insulin mediated glucose uptake	*Time varying*	$L.mU^{-1} \cdot min^{-1}$	-
G_{fast}	Patient Fasting Glucose	*Clinical*	$mmol \cdot L^{-1}$	-
EGP	Endogenous glucose production	0.96	$mmol \cdot min^{-1}$	[8]
CNS	Central nervous system glucose uptake	0.3	$mmol \cdot min^{-1}$	[8]
V_G	Glucose volume of distribution	$0.18m$	L	[8]
n_K **	Kidney clearance of insulin	0.0644	min^{-1}	[8]
n_L	Hepatic insulin clearance	0.15	min^{-1}	[8]
α_I	Saturation of liver clearance	0.0017	$L \cdot mU^{-1}$	[8]
x_L	First-pass hepatic insulin clearance	0.67	–	[8]
n_C	Insulin: Peripheral degradation	0.032	min^{-1}	[8]
V_I	Insulin volume of distribution	$0.038m$	L	[8]
n_I	Insulin trans-endothelial diffusion	0.006	min^{-1}	[8]
α_G	Saturation of insulin binding to cells	0.0154	$L \cdot mU^{-1}$	[8]
Endogenous Insulin Secretion				
k_1	C-peptide: diffusion between central and peripheral compartments	0.0478	min^{-1}	[10]
k_2		0.0516	min^{-1}	[10]
k_3 *	Clearance of C-peptide	0.0644	min^{-1}	[10]

E. Insulin Sensitivity Identification

Glucose, insulin dose and meal data enable patient-specific insulin sensitivity to be identified via integral-based methods [13, 14]. A 6-hourly insulin sensitivity was identified based on data density and to observe changes over a 24-hour period.

III. Clinical Trial

Glycaemic data was obtained from patients enrolled in a two-day pilot trial using insulin Detemir following elective cardiac surgery at St George's Hospital, Christchurch, New Zealand. Ethical consent was obtained from the NZ National Health and Disability Ethics Committee. Inclusion criteria was pre-operative HbA1c > 40 $mmol/L$. N=4 patients were enrolled to date, but 1 had consent withdrawn, giving N=3 for this study. Patient demographics are in Table 2.

Each patient received $0.25\ U/kg$ of insulin Detemir the morning of the first day, while no dose is given on the second. Blood samples were taken at -60, 30, 60 and 120 minutes around each meal, and assayed for C-peptide and insulin concentrations (Roche Elecsys), converting plasma insulin concentrations using 1 μU/mL = 6.00 pmol/L [15]. The amount eaten in each meal was estimated from a photograph before and after each meal, with nutritional information given by the hospital. Any snacks were recorded in hospital notes.

IV. Results

Identified model fit to data for Patients 1-3 are shown in Figures 2, and summarized in Table 3. Overall model fit is good for Patients 1 and 2, with the model capturing all major peaks/trough dynamics. RMS error is 1.1 – 1.4 mmol/L in these patients, with slight timing mismatch around peaks contributing to most errors.

RMS error to measured insulin data is larger, as some peak magnitudes timing mismatches mean vertical error is large, even if horizontal error is qualitatively good. This error is anticipated as no parameter is specifically fit to this insulin data, and the fit quality is merely a measure of the endogenous secretion modelled and the modelled Detemir insulin appearance. Overall, it appears no major dynamics are missing from the model.

Model fit to Patient 3 is reasonable for plasma insulin, but worse for plasma glucose. From Figure 2b) may be that plasma glucose is persistently high with very little meal response, or additional unrecorded meals are consumed. This patient also displays very low insulin secretion relative to Patients 1 and 2, and has no first phase secretion, which is typically indicative of T2D, and matches their much higher HbA1c in Table 2 of 68mmol/mol.

Focusing only on pre-diabetes Patients 1-2, identified 6-hourly insulin sensitivity is consistent with normal glucose tolerance ($10.8 \times 10^{-4}\ LmU^{-1}min^{-1}$) to impaired glucose tolerance ($6.9 \times 10^{-4}\ LmU^{-1}min^{-1}$) [16], matching their pre-diabetes HbA1c of 41 and 43 mmol/mol in Table 2 [17].

Examining endogenous insulin suppression by exogenous insulin Detemir, the total insulin secreted is compared in Table 4 for pre-diabetes Patients 1-2. Insulin secreted is similar for both days, irrespective of the presence of insulin Detemir. Meal-normalized insulin secretion in Table 4 shows secretion per carbohydrate gram (effectively insulin sensitivity) is much higher on Day 2 without insulin Determir, despite increasing recovery. Thus, adding insulin Detemir does not appear to suppress insulin secretion, and aids glucose uptake.

V. Discussion and Conclusions

The model developed here extends previous models with a novel insulin Detemir model [12] for pre-diabetes and T2D. Overall, model fit to initial data indicates the model captures all observed dynamics well. It does not initially appear that insulin Detemir has any suppressive effect on endogenous insulin production. Since only 2-4 % of the insulin Detemir is unbound at any time (~21 mU on average) any effect would likely be minimal and insufficiently large to affect pancreatic secretion [18]. Future trials should assess higher insulin Detemir doses.

Perhaps the largest error source is meal consumption estimation, which has magnitude and timing error. Insulin secretion rates were 34-240mU/min and 34-320mU/min for Patients 1-2, respectively. Secretion rates as high as 464mU/min were obtained [19] in a similar cohort, suggesting the rates here are physiologically possible. Equally, these patients are likely more insulin resistant post-surgery, which could be reflected in higher secretory rates.

TABLE II: *Patient demographics for the clinical trial.*

Patient	**Age**	**Sex**	**Weight (kg)**	**BMI (kg/m^2)**	**Bolus Size (U)**	**HbA1c (mmol/mol)**
1	73	M	88	27.2	22	41
2	74	F	72	27.1	18	43
3	75	M	88	29.1	22	68

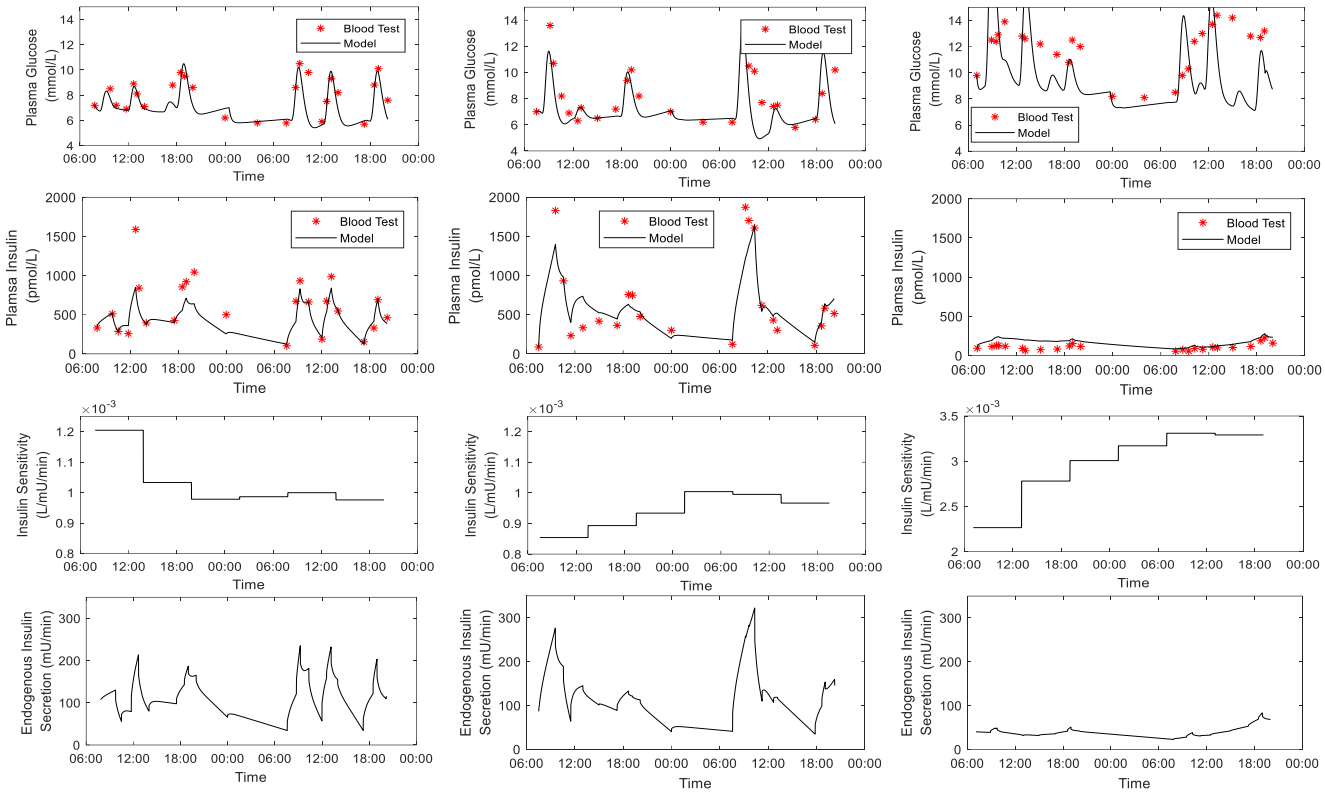
TABLE III: *RMS error from model fit to clinical data.*

Patient	Glucose RMS	Insulin RMS
1	1.105 $mmol/L$	506.0 $pmol/L$
2	1.425 $mmol/L$	553.7 $pmol/L$
3	3.13 $mmol/L$	82.1 $pmol/L$

TABLE IV: *Effect of Insulin Detemir on pancreatic function*

	Patient 1		**Patient 2**	
	Day 1	**Day 2**	**Day 1**	**Day 2**
Total insulin production (U)	85.4	87.5	101	99.4
Average secretion rate (mU/min)	117	121	143	131

Detemir dose (U)	22.0	–	18.0	–
Meal Size (g carb)	179	262	160	248
Meal-normalised production (U/g)	0.48	0.33	0.63	0.40



a) Patient 1 *b) Patient 3* *b) Patient 3*

Figure 2: Model fits to clinical data to give (from top) simulations of Plasma glucose, plasma insulin, insulin sensitivity and endogenous insulin secretion.

Overall, the model readily captures observed glucose-insulin dynamics in glucose responsive patients, and enables potentially novel approaches to early insulin use to delay onset of T2D from pre-diabetes.

REFERENCES

[1] D. R. Whiting, L. Guariguata, C. Weil, and J. Shaw, "IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030," *Diabetes Res Clin Pract*, vol. 94, pp. 311-21, Dec 2011.

[2] M. K. Dea, M. Hamilton-Wessler, M. Ader, D. Moore, L. Schaffer, M. Loftager, *et al.*, "Albumin binding of acylated insulin (NN304) does not deter action to stimulate glucose uptake," *Diabetes*, vol. 51, pp. 762-9, Mar 2002.

[3] S. Havelund, A. Plum, U. Ribel, I. Jonassen, A. Volund, J. Markussen, *et al.*, "The mechanism of protraction of insulin detemir, a long-acting, acylated analog of human insulin," *Pharm Res*, vol. 21, pp. 1498-504, Aug 2004.

[4] H. C. Gerstein, J. Bosch, G. R. Dagenais, R. Diaz, H. Jung, A. P. Maggioni, *et al.*, "Basal insulin and cardiovascular and other outcomes in dysglycemia," *N Engl J Med*, vol. 367, pp. 319-28, Jul 26 2012.

[5] W. H. Herman, "The economics of diabetes prevention," *Med Clin North Am*, vol. 95, pp. 373-84, viii, Mar 2011.

[6] M. A. Batais and P. Schantter, "Prevalence of unwillingness to use insulin therapy and its associated attitudes amongst patients with Type 2 diabetes in Saudi Arabia," *Prim Care Diabetes*, vol. 10, pp. 415-424, Dec 2016.

[7] L. Holder-Pearson, S. Bekisz, J. Knopp, P. Docherty, J. G. Chase, and T. Desaive, "Model-based Modified OGTT Insulin Sensitivity Test Design.," presented at the IFAC Symposium on Biological Medical Systems (BMS 2018), Sao Paulo, Brazil, 2018.

[8] T. F. Lotz, J. G. Chase, K. A. McAuley, G. M. Shaw, X. W. Wong, J. Lin, *et al.*, "Monte Carlo analysis of a new model-based method for insulin sensitivity testing," *Comput Methods Programs Biomed,* vol. 89, pp. 215-25, Mar 2008.

[9] C. Dalla Man, M. Camilleri, and C. Cobelli, "A system model of oral glucose absorption: validation on gold standard data," *IEEE Trans Biomed Eng,* vol. 53, pp. 2472-8, Dec 2006.

[10] E. Van Cauter, F. Mestrez, J. Sturis, and K. S. Polonsky, "Estimation of insulin secretion rates from C-peptide levels. Comparison of individual and standard kinetic parameters for C-peptide clearance," *Diabetes,* vol. 41, pp. 368-77, Mar 1992.

[11] P. Kurtzhals, S. Havelund, I. Jonassen, B. Kiehr, U. D. Larsen, U. Ribel, *et al.*, "Albumin binding of insulins acylated with fatty acids: characterization of the ligand-protein interaction and correlation between binding affinity and timing of the insulin effect in vivo," *Biochem J,* vol. 312 (Pt 3), pp. 725-31, Dec 15 1995.

[12] B. van Noorden, J. L. Knopp, and J. G. Chase, "A Subcutaneous Insulin Pharmacokinetic Model for Insulin Detemir," *Diabetes Science and Technology,* vol. (in review), pp. 12-pages (avail on request), 2019.

[13] C. E. Hann, J. G. Chase, J. Lin, T. Lotz, C. V. Doran, and G. M. Shaw, "Integral-based parameter identification for long-term dynamic verification of a glucose-insulin system model," *Comput Methods Programs Biomed,* vol. 77, pp. 259-270, Mar 2005.

[14] P. D. Docherty, J. G. Chase, and T. David, "Characterisation of the iterative integral parameter identification method," *Medical and Biological Engineering and Computing,* pp. 1-8, 2012.

[15] J. L. Knopp, L. Holder-Pearson, and J. G. Chase, "Insulin Units and Conversion Factors: A Story of Truth, Boots, and Faster Half-Truths," *J Diabetes Sci Technol,* p. 1932296818805074, Oct 13 2018.

[16] K. A. McAuley, S. M. Williams, J. I. Mann, R. J. Walker, N. J. Lewis-Barned, L. A. Temple, *et al.*, "Diagnosing insulin resistance in the general population," *Diabetes Care,* vol. 24, pp. 460-4, Mar 2001.

[17] K. A. McAuley, J. E. Berkeley, P. D. Docherty, T. F. Lotz, L. A. Te Morenga, G. M. Shaw, *et al.*, "The dynamic insulin sensitivity and secretion test--a novel measure of insulin sensitivity," *Metabolism,* 2011.

[18] J. E. Liljenquist, D. L. Horwitz, A. S. Jennings, J. L. Chiasson, U. Keller, and A. H. Rubenstein, "Inhibition of insulin secretion by exogenous insulin in normal man as demonstrated by C-peptide assay," *Diabetes,* vol. 27, pp. 563-70, May 1978.

[19] R. P. Eaton, R. C. Allen, D. S. Schade, K. M. Erickson, and J. Standefer, "Prehepatic insulin production in man: kinetic analysis using peripheral connecting peptide behavior," *J Clin Endocrinol Metab,* vol. 51, pp. 520-8, Sep 1980.