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Tracking the progression to type 2 diabetes with a proportional-derivative insulin secretion model

Nor Azlan Othman[a], Paul D. Docherty[b,*], Nor Salwa Damanhuri[a], J. Geoffrey Chase[b]

[a] Faculty of Electrical Engineering, Universiti Teknologi MARA (UiTM), Penang Campus, Permatang Pauh 13500 Penang, Malaysia
[b] Department of Me chanical Engineering, Centre for Bio-Engineering, University of Canterbury, Private Bag 4800 Christchurch 8054, New Zealand

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ABSTRACT

Background: Modelling insulin secretion as a function of peripheral C-peptide levels by mathematical deconvolution is widespread. However, the measurement resolution for successful deconvolution and high cost of C-peptide assays means measurement of insulin secretion can only be undertaken in small scale research endeavours. This research models the nature of insulin secretion (U_N) during the pathogenesis of type 2 diabetes.

Methods: A proportional-derivative U_N model is based on the physiological, closed-loop insulin secretion response to increasing glucose (ϕ_D) and glucose excursions (ϕ_P). A total of 204 dynamic insulin sensitivity and secretion test (DISST) data sets from 68 participants in a 10-week dietary intervention trial were used to determine ϕ_D and ϕ_P values. The resulting gain values are used to classify subjects and thus the evaluation of U_N over increasing insulin resistance.

Results: Participants with impaired fasting glucose ($G_O > 5.56$ mmol L^{-1}) had a lower median ϕ_D value that becomes almost equal to ϕ_P. In contrast, NGT participants ($G_O < 5.56$ mmol L^{-1}), ϕ_D that tended to be much greater than ϕ_P. Thus, as the metabolic state of a participant moves from NGT to pre-diabetes, the participant is loses first phase insulin burst secretion. The resulting gains are classified by easily measured basal glucose.

Conclusions: The simplicity of this PD U_N model in a DISST model framework provides clear relationship between the U_N profile and the readily available metabolic state of each participant. These relationships could significantly improve the cost and resolution of model-based tests like the DISST.

1. Introduction

Deconvolution of C-peptide concentrations is effectively considered the gold-standard method for quantifying endogenous insulin secretion (U_N), and is thus used in many studies (Eaton, Allen, Schade, Erickson, & Standefer, 1980; Polonsky et al., 1986; Van Cauter, Mestrez, Sturis, & Polonsky, 1992). It assumes that insulin and connecting-peptide (C-peptide) are co-secreted at equimolar rates from the pancreas (Rubenstein, Clark, Malani, & Steiner, 1969). Unlike C-peptide, acquiring plasma insulin measurements to precisely predict U_N will lead to false information as insulin undergoes substantial, subject-specific first pass hepatic extraction before reaching the peripheral circulation (Hovorka & Jones, 1994; Polonsky et al., 1986). In addition, insulin is cleared subsequently by the liver, kidney and peripheral uptake, all of which can be variable and hard to quantify. In contrast, C-peptide is cleared predominantly by the kidney, which is a relatively consistent pathway. Thus, utilising C-peptide data within a model-based framework is a robust means of estimating endogenous insulin secretion.

Although the use of C-peptide has proven a better means of estimating U_N (Pacini & Mari, 2003), C-peptide measurements are time-consuming and expensive (Lin et al., 2010). Further, accurate deconvolution requires reasonably high resolution data. The cost can significantly reduce the economic viability of metabolic tests that accurately capture the pathogenesis of diabetes (Docherty et al., 2010; Dochertyet al., 2011). Hence, there remains significant scope to realize the potential benefit in further understanding insulin secretion in the pathogenesis of diabetes.

This study evaluates a proportional-derivative (PD) control model's ability to link the patient-specific U_N characteristics to glucose excursions and the pathogenesis of diabetes (Breda, Cavaghan, Toffolo, Polonsky, & Cobelli, 2001; Cobelli et al., 2007; Othman, Docherty, & Chase, 2014; Othman, Docherty, Damanhuri, & Chase, 2015; Othman, Docherty, Jamaludin, & Chase, 2012; Overgaard, Jelic, Karlsson,

* Corresponding author.
E-mail addresses: azlan253@ppinang.uitm.edu.my (N.A. Othman), paul.docherty@canterbury.ac.nz (P.D. Docherty), norsalwa071@ppinang.uitm.edu.my (N.S. Damanhuri), geoff.chase@canterbury.ac.nz (J.G. Chase).

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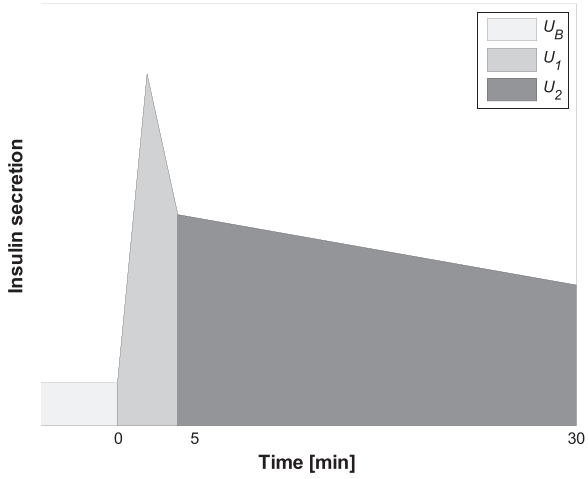

Fig. 1. Illustration of insulin secretion from pancreatic β-cell. UB is defined as basal insulin, U_1 is first phase and U_2 is the second phase of insulin secretion.

Henriksen, & Madsen, 2006; Toffolo, Cefalu, & Cobelli, 1999). Physiologically, the rate of insulin secretion is proportional to glucose levels and the positive gradient of glucose (Cherrington, 1999). The derivative gain (ϕ_D) and proportional gain (ϕ_P) identified by a PD U_N model mimic these physiological characteristics and capture what is clinically denoted as first and second phase of insulin secretion, respectively. In particular, studies have shown that insulin is secreted in biphasic patterns (Cerasi & Luft, 1967; Cerasi, 1967; Curry, Bennett, & Grodsky, 1968). The U_N profile in response to intravenous (IV) glucose challenge shows these phases more prominently than a meal or oral dose glucose load. The first phase occurs rapidly due to a sudden change in glucose level after glucose stimulation and only lasts for few minutes (Curry et al., 1968). Unlike first phase, the second phase secretion lasts longer, as it is gradually released by the pancreatic β-cells to reduce the remaining elevated glucose level towards a safe levels (Curry et al., 1968). Fig. 1 shows a schematic U_N with first and second phase secretion.

The relationship between the characteristics of first and second phase U_N with type 2 diabetes (T2D) is well founded by prior studies (Bunt, Krakoff, Ortega, Knowler, & Bogardus, 2007; Del Prato, & Tiengo, 2001; Pratley & Weyer, 2001; Weyer, Bogardus, Mott, & Pratley, 1999). The loss of first phase secretion and reduced second phase secretion define the U_N characteristics of observed in individuals with T2D (Cerasi & Luft, 1967; Davis et al., 1993). Since the PD U_N model captures the pancreatic response to glucose, associating ϕ_D and ϕ_P to first and second phase secretion provides an insight gain towards understanding the pathogenesis of type 2 diabetes. In particular, the changes in ϕ_D and ϕ_P, as diabetes develops, should illustrate these observed changes in secretion pattern.

This paper investigates the accuracy of this previously proposed PD control U_N model in identifying and discriminating the U_N profile in terms of insulin sensitivity and other metrics for normal glucose tolerance (NGT) and impaired fasting glucose (IFG) participants. In particular, relating changes in PD model parameters between these two groups. A successful outcome would indicate a clear trend in subject-specific ϕ_D and ϕ_P values and in their ability to denote the stage of the test participant on the pathogenesis of type 2 diabetes.

2. Methods

2.1. Participants and data

A total of 94 female participants were recruited from the Otago region of New Zealand to take part in a 10-week dietary intervention trial defined in Te Morenga et al. Morenga, Williams, Brown, and Mann (2010). The median participant age was 42.5 years (IQR 34.5–50.5) and the median BMI was 32.3 kg/m^2 (27.9–36.9). Participants were screened to capture those of greatest risk of developing type 2 diabetes. Hence, inclusion criteria required a body mass index (BMI) greater than 25, or greater than 23 and a family history of T2D, or ethnic disposition toward T2D. Participants were excluded if they had a major illness, including established diabetes, at the time of testing. In total, 68 participants provided 204 full test DISST data sets at week 0, week 4 and week 10 of the intervention.

2.2. Clinical procedure

Participants reported in the morning after at least 10 h of overnight fasting. Each participant had a cannula inserted in the ante-cubital fossa (vein in inner elbow) for blood sampling and administration of glucose and insulin boluses. Blood samples were drawn at t=0, 5, 10, 15, 20, 25, 30, 35, 40 and 50 min. A 10g IV glucose bolus (50% dextrose and 50% saline) was administered via the venous catheter at t=6 min. 1U of IV insulin was administered at t=16 min. Blood samples were centrifuged at 1650g before being assayed for plasma glucose (Enzymatic glucose hexokinase assay, Abbott Labs, Illinois USA - reported CV 0.5%), insulin and C-peptide concentration (ELISA Immunoassay, Roche, Mannheim, Germany – reported CV 1.5%).

2.3. Physiological models

2.3.1. Dynamic Insulin Sensitivity and Secretion Test (DISST) model

The DISST model provides quantitative measures of both *SI* and U_N (Lotz et al., 2010; McAuley, Mann, Chase, Lotz, & Shaw, 2007; McAuley et al., 2011), and was derived, in part, from the Minimal Model of glucose dynamics (Bergman, Ider, Bowden, & Cobelli, 1979). The DISST model identifies the U_N profile via the deconvolution of C-peptide assays (Cobelli & Caumo, 1998; Hovorka & Jones, 1994; Hovorka, Koukkou, Southerden, Powrie, & Young, 1998; Van Cauter et al., 1992). Tracer elements were not used in this study as U_N values are well-estimated using deconvolution alone (Polonsky et al., 1986). The DISST model is defined:

C-peptide Pharmaco-Kinetics:

$$\dot{C}=-(k_1+k_3)C+k_2Y+\frac{U_N}{V_p} \tag{1}$$

$$\dot{Y}=-k_2Y+k_1C \tag{2}$$

Insulin Pharmaco-Kinetics:

$$\dot{I}=-n_kI-n_L\frac{I}{1+\alpha_I I}-\frac{n_I}{V_p}(I-Q)+\frac{U_{ex}}{V_p}+(1-x_L)\frac{\xi U_N}{V_p} \tag{3}$$

$$\dot{Q}=-\left(n_C+\frac{n_I}{V_q}\right)Q+\frac{n_I}{V_q}I \tag{4}$$

and Glucose-Insulin Pharmaco-Dynamics:

$$\dot{G}=-p_{gu}(G-G_B)-S_I(GQ-G_BQ_B)+\frac{P_t}{V_g} \tag{5}$$

where equation nomenclature is shown in Table 1.

2.3.2. Proportional-derivative (PD) endogenous insulin secretion (U_N) model

A physiologically realistic nonlinear, switching PD U_N model was proposed to estimate U_N as a function of increasing glucose (derivative control, ϕ_D) and glucose above basal (proportional control, ϕ_P).

$$U_N=U_B+\phi_P(G-G_B)+\phi_D\langle\dot{G}\rangle \tag{6}$$

where U_B is basal insulin [pmol·min^{-1}]; ϕ_P and ϕ_D are the proportional, and derivative gains [pmol·L·mmol^{-1}·min^{-1} and pmol·L·mmol^{-1}, respectively]. Note that $\langle\dot{G}\rangle$ indicates the coefficient of ϕ_D is set to zero if