Developin_________ ating a new comprehensive glucoseinsulin pharmacokinetics and pharmacodynamics model

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A thesis submitted for the degree of

Doctor of Philosophy. 350

in

Mechanical Engineering

at the

University of Canterbury,

Christchurch, New Zealand

24 June 2013

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Nomenclature

Acronyms and abbreviations

| ACCP/SCCM | American College of Chest Physicians/Society of Critical Care Medicine |
|-----------|---|
| ADA | American Diabetes Association |
| APACHE | Acute Physiology and Chronic Health Evaluation |
| ARF | Acute Renal Failure |
| ATP | Adenosine Triphosphate |
| AUC/c-ROC | Area Under the Curve |
| BMI | Body Mass Index |
| BSA | Body Surface Area |
| CAVH | Continuous Arteriovenous Haemofiltration |
| CAVHD | Continuous Arteriovenous Haemodialysis |
| CGM | Continuous Glucose Monitoring |
| CI | Confidence Interval |
| CIGMA | Continuous Infusion Glucose Model Assessment |
| CV | Coefficient of Variance |
| CVD | Cardiovascular Disease |
| DISST | Dynamic Insulin Sensitivity and Secretion Test |
| DPP-4 | Dipeptidyl Peptidase-4 |
| ECLIA | Enhanced Chemiluminescence Immunoassay |
| EGP | Endogenous Glucose Production |
| EIC | Euglycaemic CLAMP |
| EN | Enteral |
| FS-IVGTT | Frequently Sampled-Intravenous Glucose Tolerance Test |
| GC | Glycaemic Control |
| GE | Glucose Effectiveness |
| GFR | Glomerular Filtration Rate |
| GIP | Glucose-dependent Insulinotropic Polypeptide |
| GLP-1 | Glucagon Like Peptide-1 |
| HD | Haemodialysis |
| HDL | High Density Lipoprotein |
| HOMA | Homeostasis Model Assessment |
| ICING | Intensive Control Insulin-Nutrition-Glucose |
| ICU | Intensive Care Unit |
| IFG | Impaired Fasting Glucose |
| IGT | Impaired Glucose Tolerance |
| IIM | Iterative Integral Method |
| IQR | Interquartile Range |
| IR | Insulin Resistance |

| ISI | Insulin Sensitivity Index |
|--------|--|
| IV | Intravenous |
| IVGTT | Intravenous Glucose Tolerance Test |
| MATLAB | Matrix Laboratory |
| MGTT | Meal Glucose Tolerance Test |
| MM | Minimal Model |
| NGT | Normal Glucose Tolerance |
| OGTT | Oral Glucose Tolerance Test |
| PD | Proportional Derivative |
| PK-PD | Pharmacokinetic-Pharmacodynamic |
| PN | Parenteral |
| PS | Polysulfone |
| SI | Insulin Sensitivity |
| SPRINT | Specialized Relative Insulin and Nutrition Titration |
| T2D | Type 2 Diabetes |
| T2DM | Type 2 Diabetes Mellitus |
| TGC | Tight Glycaemic Control |

Abstract

Type 2 diabetes has reached epidemic proportions worldwide. The resulting increase in chronic and costly diabetes related complications has potentially catastrophic implications for healthcare systems, and economics and societies as a whole. One of the key pathological factors leading to type 2 diabetes is insulin resistance (*IR*), which is the reduced or impaired ability of the body to make use of available insulin to maintain safe glucose concentrations in the bloodstream.

It is essential to understand the physiology of glucose and insulin when investigating the underlying factors contributing to chronic diseases such as diabetes and cardiovascular disease. For many years, clinicians and researchers have been working to develop and use model-based methods to increase understanding and aid therapeutic decision support. However, the majority of practicable tests cannot yield more than basic metrics that allow only a threshold-based assessment of the underlying disorder.

This thesis gives an overview on several dynamic model-based methodologies with different clinical applications in assessing glycaemia via measuring effects of treatment or medication on insulin sensitivity. Other tests are clinically focused, designed to screen populations and diagnose or detect the risk of developing diabetes. Thus, it is very important to observe sensitivity metrics in various clinical and research settings.

Interstitial insulin kinetics and their influence on model-based insulin sensitivity observation was analysed using data from the clinical pilot study of the dynamic insulin sensitivity and secretion (DISST) test and the glucose-insulin PK-PD models. From these inputs, a model of interstitial insulin dose-response that best links insulin action in plasma to response in blood glucose levels was developed. The critical parameters influencing interstitial insulin pharmacokinetics (PKs) are saturation in insulin receptor binding (α_G) and the plasma-interstitium diffusion rate (n_i). Population values for these parameters are found to be [α_G , n_i]=[0.05,0.055].

Critically ill patients are regularly fed via constant enteral (EN) nutrition infusions. The impact of incretin effects on endogenous insulin secretion in this cohort remains unclear. It is hypothesised that the identified S_I would decrease during interruptions of EN and would increase when EN is resumed, where, for short periods around transition, the true patient S_I would be assumed constant. The model-based analysis was able to elucidate incretin effects by tracking the identified model-based insulin sensitivity (S_I) in a cohort of critically ill patients. Thus, changes in model-based S_I given the fixed assumed endogenous secretion by the model would support the presence of an EN-related incretin effect in the population of non-diabetic, critically ill patients studied.

The PD feedback-control model of U_{en} was designed to investigate endogenous insulin secretion amongst subjects with different metabolic states and levels of insulin resistance. The underlying effects that influence insulin secretion i.e. incretin effects were also defined by tracking the control model gain/response and the identified insulin sensitivity (S_I) using intravenous (IV) bolus and oral glucose responses of insulin sensitivity tests. This new PD control model allowed the characterisation of both static (basal) and dynamic insulin responses, which defined the pancreatic β -cell glucose sensitivity parameters. However, incretin effects were unobserved during oral glucose responses as the PD control gains failed to simulate the true endogenous insulin secretion due to potentially inaccurate glucose appearance rates and low data resolution of glucose concentrations.

The net effect of haemodialysis (HD) treatment on glycaemic regulation and insulin sensitivity in a critically ill cohort was investigated. It was hypothesized that the observed S_I would decrease during HD due to enhanced insulin clearance compared to the model, and would be recaptured again when HD is stopped. The changes in model-based S_I metric at HD transitions in a cohort of critically ill patients were evaluated. Significant changes of -29% in model-based S_I was observed during HD therapy. However, there were insignificant changes when HD treatment was ended. Thus, the changes in model-based S_I would thus offer a unique observation on insulin kinetics and action in this population of critically ill patients with ARF that would better inform metabolic care.

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Chapter 1. Introduction

The number of people with diabetes has significantly increased in recent years to approximately 350 million people worldwide (Chen *et al.* 2011). Chronic hyperglycaemia is the main characteristic of diabetes and is directly associated with morbidity and mortality (Capes *et al.* 2000; Krinsley 2003; Krinsley 2004; Van den Berghe *et al.* 2001). In 2004, an estimated 3.4 million people died due to hyperglycaemia (ADA 2006a). Thus, it is suggested that diabetes has reached epidemic proportions, with catastrophic implications on quality of life, healthcare costs and population as a whole (Bonow and Gheorghiade 2004; Chiu *et al.* 2001; King 1999).

The general symptoms of diabetes can be alleviated with glycaemia control protocols in intensive care unit (ICU), which are reported to reduce the risk of other metabolic complications i.e. cardiovascular, sepsis, acute renal failure, and etc. (Chase *et al.* 2008; Evans *et al.* 2011; Krinsley 2004; Van den Berghe *et al.* 2001). Also, understanding the underlying metabolic disorders that contribute to the pathogenesis of diabetes can potentially prevent the risk of developing this disease at the very early stage or provide the best approach to treat diabetes before it becomes chronic. This chapter discusses the overall prevalence, its development and underlying causes of diabetes. Review on its current clinical diagnosis assessment methods and glycaemic control protocols for critically ill patients are also presented.

1.1 Pathogenesis Type II Diabetes Mellitus (T2DM)

The pathogenesis of T2DM is a more gradual process than type 1 diabetes. It generally starts with the pre-diabetes stages of impaired glucose tolerance (IGT) and impaired fasting glucose (IFG), before a clinical classification of diabetes can be made. The progression of this disease is often undiagnosed and untreated for many years, until first health complications start to appear. The physical symptoms that usually occurred in T2DM are listed as follows:

• Dehydration and frequent urination. As blood glucose concentration builds up in the bloodstream, fluid is absorbed from the tissues which cause dehydration. Thus, it increased the fluid consumption and urinates more frequently than normal.

- Increased appetite. Without enough insulin to bind with cells in peripheral tissues and muscles causes' energy depletion that triggers intense appetite.
- Weight loss. The body uses alternative fuels stored in muscle and fat as source of energy due to decreased glucose metabolism in the bloodstream.
- Fatigue. The body becomes tired and exhausted as the cells are deprived of glucose.
- Blurred vision. This symptom only occurs when hyperglycaemia causes excessive fluid appearance in the eyes lenses.
- Low immunity system. T2DM affects the body's ability to heal and resist infections. Later, it may cause sepsis if it is untreated.

Typically, T2DM is not recognised early enough to intervene before permanent damage has begun to occur, and is thus often diagnosed only when treating its symptoms or complications at later levels (Gastaldelli *et al.* 2004; Kleinfield 2006). This late diagnosis is due to the nature of the disease development, where noticeable symptoms do not arise until significant irreversible damage has occurred. With accurate early diagnosis pre-diabetic states could potentially identified up to 3-5 years earlier (Andersson *et al.* 2009; Clark *et al.* 2000; Pannala *et al.* 2009) which can significantly reduce the onset of further damage and complications.

T2DM is increasingly diagnosed among children, adolescents and younger adults (Hossain *et al.* 2007). The causes of this epidemic disease are embedded in a very complex group of genetic besides the integrated between quality of life and environmental influences. Given that both insulin secretion and its kinetic are under genetic control, failure of β -cell function and/or *IR* could theoretically be the primary factors in T2DM (DeFronzo and Ferrannini 1991; Kahn 2003; Poulton *et al.* 2002; Staiger *et al.* 2009; Stumvoll *et al.* 2005). This common aspect presumably reflects the development of *IR* at the peripheral and receptor level, particularly in the liver, skeletal muscle and heart (Andrews and Walker 1999; Reaven 1988; Shulman 2000).

The chronological treatment of T2DM consists first of lifestyle changes to increase insulin sensitivity. Increases in exercise with healthier diet and weight loss are proven to increase insulin sensitivity and thus reduce the prevalence or impact of T2DM (Duncan *et al.* 2003; McAuley *et al.* 2002; Nishida *et al.* 2004; Tuomilehto *et al.* 2001). This is may be combined with medication,

such as thiazolidinedionesn (Rosiglitazone), biguanides (Metformin) or sulfonylureas (Glyburdie) to enhance insulin sensitivity or stimulate the pancreas secretion (Kahn *et al.* 2006). Lastly, insulin replacement therapy (i.e. exogenous insulin input via insulin pump) as in type 1 diabetes, is required to maintain glucose homeostasis (Hermansen *et al.* 2002; Pickup and Keen 2002; Schaumberg *et al.* 2005; Steil *et al.* 2006)

1.2 Development of model-based S_I test

The model-based insulin sensitivity methods have shown significant ability to diagnose and characterise pre-diabetic state (Beard *et al.* 1986; Bergman *et al.* 1987; Boston *et al.* 2003; Chase *et al.* 2008; Lotz 2007; Mari *et al.* 2001a; McAuley *et al.* 2011; Pacini and Bergman 1986; Wallace and Matthews 2002). Model-based approaches measure the physiological effects that explain the causes to progression of diabetes. Model-based S_I tests typically use empirical methods, mostly regression models that are designed to correlate well with certain gold standard test metrics i.e. euglycaemic/hyperglycaemic clamp (EIC) (Beard *et al.* 1986; Bergman *et al.* 1987; DeFronzo *et al.* 1979; Mari *et al.* 2001a; Pacini and Bergman 1986).

If fasting metrics are used insulin sensitivity is only quantified during a fasting state which may be different to postprandial sensitivity. It is also assumed that the insulin secretion from β -cells can be measured by sampling C-peptide concentrations (Pacini and Mari 2003). The elevated insulin concentrations can cause endogenous glucose production inhibition (EGP). The level of inhibition can be measured with the additional use of glucose tracers (Caumo and Cobelli 1993). Thus, S_I metrics can be different to the real-observed during the dynamic or hyperglycaemic state used in other applications (Scheen *et al.* 1994) as the total S_I is defined as the total amount of insulin sensitivity at peripheral cells and liver.

It is important to model all the kinetic behaviour of insulin and glucose including: insulin clearance, endogenous glucose production, endogenous insulin secretion and to segregate the dynamics (i.e. incretin effects) to fully describe the important aspects of the true metabolic system. Figure 1.1 shows an overview of the physiological effects that can be measured by S_I tests. However, these effects can only be captured by the model depending on the design and application of the tests.



Figure 1.1 Overview of the physiological effects measured by insulin sensitivity tests. Depending on the design of the test, it can measure either one, a combined effect if two, or all three of these effects. The dashed lines indicate a mediated or enhanced effect.

The main effects contributing to insulin dependent glucose uptake (in Figure 1.1) which reflect the insulin sensitivity are the sensitivity of tissue cells to bind insulin (peripheral sensitivity), the effect of insulin on the liver to secrete glucose production (hepatic sensitivity), and the ability of the pancreas to produce insulin with increase in glucose concentration (β -cell function). These effects are time varying and are different in fasting or perturbed states (Scheen *et al.* 1994). Depending on the structural design of the chosen method to assess S_I and its assumptions, one or more of these effects can be combined in the assessment. Thus, different clinical and physiological interpretations can be delivered depending on varying results obtained from the chosen approach.

1.3 Model-based glycaemic control protocol

It is reported that model-based glycaemic control (GC) protocols ensure a reduction in hypoglycaemia in the ICU (Chase *et al.* 2007; Chase *et al.* 2008; Evans *et al.* 2011; Hovorka *et al.* 2007; Le Compte *et al.* 2009). The motivation of these protocols is to reduce clinical burden in ICU and also lessen the chronic outcomes due to organ failure, which increased morbidity and thus mortality. Model-based control relies on a physiological model that captures the glucose-

insulin system dynamics that accurately predict blood glucose, given specific insulin and glucose inputs. A control algorithm can use these predictions to select optimal insulin and nutrition interventions for forthcoming periods.

The potential of models for managing glycaemic levels in critically ill patient is thus becoming realised. However, few models have been clinically validated. For most models, the primary form of validation has been simple fitting of the model to match clinical data (Carson and Cobelli 2001). Occasionally, more rigorous prediction validation, which tests the models ability to predict the outcome of a known intervention on retrospective clinical data (or in a clinical trial) is used. However, only a few clinically validated models can predict within clinically acceptable ranges (Chassin *et al.* 2004; Lotz *et al.* 2008; Pielmeier *et al.* 2010; Plank *et al.* 2006; Wong *et al.* 2006).

Despite its clinical uses, glycaemic control (GC) in ICU also introduced secondary benefits. Studies by Weekers *et al.* (2003) and Langouche *et al.* (2005) indicate that glycaemic control reduces glucotoxicity due to high blood glucose, which in turn reduces oxidative stress and superoxides, which are stress hormone responses that cause damage to the endothelium and vascular walls.

Simple model-based GC protocols have been successfully developed and piloted (Chase *et al.* 2008; Chee *et al.* 2002; Evans *et al.* 2011; Fisk *et al.* 2012; Plank *et al.* 2006; Shaw *et al.* 2006). These model-based methods are able to identify evolving patient-specific parameters and tailor therapy appropriately. The principal of model-based control uses a physiological model that relies on a single, time-varying parameter, in this case S_I , to capture the patient-specific glycaemic response to insulin. As an identified parameter, S_I is prone to capturing other dynamics and metabolic effects which can be used to quantify metabolic dysfunctions and variability in critically ill patients. Although maintaining safe, effective model-based glycaemic control in critically ill patients has proven difficult, due to considerable inter- and intra- patient variability, it may offer the most practical, robust, adaptive and patient-specific solution to manage this issue. Success is thus a function of the model's ability to accurately capture the dynamics of insulin kinetic over time in the highly variable critically ill patient.

1.4 Preface

The objective of this thesis is to understand and validate various pharmacokinetic and pharmacodynamic (PK-PD) models in wider research and clinical settings and present analyses of several important insulin kinetic and metabolic dysfunctions which affect the model-based insulin sensitivity.

This thesis focuses on the kinetic parameters of the (PK-PD) models that affect the insulin secretion, insulin transport kinetics, incretins, and insulin clearance. Additionally, the impact of haemodialysis treatment in critically ill patients and the renal insulin clearance and insulin secretion were also presented. A brief overview of the thesis includes:

Chapter 2 presents the physiology of plasma insulin, glucose, C-peptide and incretins.

Chapter 3 reviews current model-based S_I assessments used in research and clinical settings and its applications.

Chapter 4 investigates the modelling of interstitial insulin actions, using different clinicalvalidated PK and PD models with DISST data.

Chapter 5 quantify and analyses the incretin effects of critically ill patients that underwent the SPRINT protocol.

Chapter 6 develops a control model for pancreatic insulin secretion as a function of glucose excursions.

Chapter 7 assesses the impact of haemodialysis (HD) therapy on insulin kinetics and action in critically ill patients with acute renal failure.

Chapter 8 and 9 summaries the key aspects of the thesis and present possible future applications for this research.

6

Chapter 2. Physiology of Plasma Insulin, Glucose, C-peptide and Incretins

This chapter describes the physiology and biochemical characteristics of insulin, glucose, C-peptide and incretin. These effects are captured in dynamic models that seek to segregate the dynamic effects of insulin sensitivity, insulin secretion and other metabolic effects. Hence, it provides foundation of the necessary basic knowledge needed to create effective, realistic models.

2.1 Glucose

Glucose ($C_6H_{12}O_6$) is a monosaccharide used as the main source of energy in the body. It is oxidised in the cells to generate adenosine triphosphate (ATP) molecules which in turn provides energy to the cell (Guyton and Hall 2000). Glucose is transported around the body passively in the bloodstream. It also can be diffusively without insulin taken up by cells in the brain and the central nervous system, as they are highly permeable to glucose. However, muscle, adipose tissue cells and intestinal cells contribute to a majority of the total uptake. If available in abundance, glucose is stored by the liver and peripheral cells as glycogen for future use (Guyton and Hall 2000; Zierler 1999). Most of the body's cells require the hormone insulin to mediate glucose uptake (Despopoulos and Silbernagl 2003; Guyton and Hall 2000). Thus, insulin acts as a biochemical signal that unlocks cellular pathways of cellular glucose uptake, rather than as an integral part of that uptake. Hence, this uptake is referred to as insulin-mediated.

Glycogenesis is the process of storing excess circulating glucose as glycogen in the liver. If glycogen stores are saturated, glucose is converted into fat and stored in the liver and in fat cells in the adipose tissue. These processes can be reversed when the energy demand is high. Glucose is rapidly released from glycogen via the glycogenolysis process if glycogen stores are used, once fat is used via the gluconeogenesis process with amino acids to form glucose (Guyton and Hall 2000; Zierler 1999).

Both glycogenolysis and gluconeogenesis are commonly grouped under and described as endogenous glucose production (EGP) (Zierler 1999). EGP is tightly regulated in the healthy body to maintain basal (minimum) blood glucose concentration. EGP represents net glucose produce by the body, primarily by the liver, and released into the blood (Cherrington 1999). EGP is suppressed when blood glucose concentration is considerably high due to external glucose appearance through meals or to a lesser extent via intravenous bolus (Caumo and Cobelli 1993; Jefferson *et al.* 2001; Pretty 2012). However, low glucose concentrations inverse the process by stimulating glucagon secretion via pancreatic α -cells, which activates glycogenolysis and thus rapidly increases glucose concentrations to prevent hypoglycaemia.

The rate of endogenous glucose production is a function of both stimulus and availability of substrates. In reality, EGP is modulated by the interaction of many hormones in response to metabolic dysfunctions that cause insulin sensitivity irregularities (Gelfand *et al.* 1984; Mizock 2001). As tissue cells fail to respond adequately to insulin, blood glucose concentrations rise. Normally, the liver helps regulate glucose concentrations by reducing glucose production in the presence of insulin. However, this may not occur in T2DM due to insulin resistance that reduced glycogen synthesis and storage and a failure to suppress glucose production. In critical illness, this lack of suppression of EGP is enhanced (Capes *et al.* 2000; McCowen *et al.* 2001; Thorell *et al.* 2004).

The body naturally regulates blood glucose levels as a part of metabolic homeostasis. It is suggested that healthy fasting blood glucose concentration ranges between 4.4-5.1 mmol.L⁻¹ (80-92 mg.dL⁻¹). Prolonged malnutrition or exposure to insulin can result in mild hypoglycaemia (low blood glucose <4.0 mmol.L⁻¹ or 72 mg.dL⁻¹). Severe hypoglycaemia (<2.2 mmol.L⁻¹ or 40 mg.dL⁻¹) can limit the availability of energy to the brain and nervous system that can cause unconsciousness or death. Alternatively, hyperglycaemia is also dangerous and occurs when blood glucose is elevated above safe levels (>11.1 mmol.L⁻¹ or 200 mg.dL⁻¹) with mild hyperglycaemia is defined as BG>7.0 mmol.L⁻¹ (125 mg.dL⁻¹). A subject with a fasting blood glucose range between 5.6 and 7 mmol.L⁻¹ can be diagnosed with impaired glucose tolerance (IGT), while >7 mmol.L⁻¹ (125 mg.dL⁻¹) can diagnose type 2 diabetes. Prolonged hyperglycaemia is highly toxic to a wide range of tissues and can result in diabetic retinopathy leading to partial blindness; and

decay of peripheral capillaries which may finally require body parts be amputated. Importantly, a continuous glucose homeostasis to normal levels is essential for positive on-going health benefits, and is equally true for hyperglycaemic critically ill patients.

2.2 Plasma Insulin

Insulin is a hormone secreted by the pancreas within the β -cells of the islets of Langerhans. Within the islets of Langerhans, β -cells constitute 65-80% of all the cells. Insulin has a leading role in maintaining glucose homeostasis. It enables glucose uptake by muscle and adipose tissue cells, regulates storage and release of glucose in the liver and promotes fat synthesis and storage (Guyton and Hall 2000; Jefferson *et al.* 2001). The pancreas secretes plasma insulin into the portal vein, where it first passes through the liver and subsequently enters systemic circulation. Glucose uptake is activated once plasma insulin is distributed to interstitial fluid, where it binds to cell-membrane receptors (Jefferson *et al.* 2001) as shown in Figure 2.1

Insulin secretion by the pancreas is bi-phasic in healthy subjects (Guyton and Hall 2000; Jefferson *et al.* 2001; Prager *et al.* 1986; Sherwin *et al.* 1974). The first phase is a release of stored insulin in response to significant changes in glucose concentration. The magnitude of the first phase insulin secretion is typically to the rate of changes in glucose and the glucose gradient between the periphery and the portal vein (Cherrington 1999).

The second phase is a prolonged, slow release of newly formed insulin dependent on glucose concentration. When the first phase insulin secretion is diminished, blood glucose concentrations will increase significantly right after oral ingestion. The pancreas compensates for this rise by increasing the second phase insulin secretion, which eventually brings blood glucose concentrations back to normal. However, these high levels of glucose and insulin in the bloodstream may damage the β -cells and further impair their ability to function. As a result, hyperglycaemia and T2DM occur in conjunction with hyperinsulinemia as a result of increased insulin resistance.

This response to glucose can be broadly modeled using a proportional-derivative (PD) feedback controller. This approach has been used to attempt closed loop control of diabetes and for tight glycaemic control (TGC) for critically ill patients (Chase *et al.* 2006; Chee *et al.* 2003; Steil *et al.* 2006). Its popularity in representing insulin secretion is the basis for its use in glycaemic controllers.



Figure 2.1 Schematic of insulin binding to receptors on tissue cells to activate glucose uptake. (Figure taken from medicinexplained.blogspot.co.nz).

Circulating insulin is mainly cleared through by the liver, accounting for up to 60% of total insulin clearance (Duckworth *et al.* 1988; Ferrannini and Cobelli 1987; Sherwin *et al.* 1974). Approximately 30-60% of endogenous insulin is extracted by the liver in the first pass after it is released into the portal vein (Duckworth *et al.* 1988; Ferrannini and Cobelli 1987; Prager *et al.* 1986; Sherwin *et al.* 1974; Toffolo *et al.* 2006). This mechanism allows a fast response and control insulin circulation and kinetics. Insulin is also cleared by the kidney (Duckworth *et al.* 1998; Mak 1995; Rabkin *et al.* 1984) and through cellular degradation after binding to allow glucose uptake in the periphery (Guyton and Hall 2000; Jefferson *et al.* 2001). Insulin has two different half-lifes at 4-6 minutes and 20-30 minutes (Duckworth *et al.* 1998; Turnheim and Waldhausl 1988).