

Pharmacokinetic/Pharmacodynamic Modelling in Diabetes Mellitus

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Abstract

Diabetes mellitus is a major health risk in many countries, and the incidence rates are increasing. Diverse therapeutic agents are applied to treat this condition. Since 1960, numerous mathematical models have been developed to describe the glucose-insulin system, analyse data from diagnostic tests and quantify drug effects. This review summarizes the present state-of-the-art in diabetes modelling, with a focus on models describing drug effects, and identifies major strengths and limitations of the published models.

For diagnostic purposes, the minimal model has remained the most popular choice for several decades, and numerous extensions have been developed. Use of the minimal model is limited for applications other than diagnostic tests. More mechanistic models that include glucose-insulin feedback in both directions have been applied. The use of biophase distribution models for the description of drug effects is not always appropriate. More recently, the effects of various antidiabetic agents on glucose and insulin have been modelled with indirect response models. Such models provide good curve fits and mechanistic descriptions of the effects of antidiabetic drugs on glucose-insulin homeostasis. These and other types of models were used to describe secondary drug effects on glucose and insulin, and effects on ancillary biomarkers. Modelling of disease progression in diabetes can utilize indirect response models as a disturbance of homeostasis.

Future needs are to include glucose-insulin feedback more often, develop mechanistic models for new drug groups, consider dual drug effects on complementary subsystems, and incorporate elements of disease progression.

Diabetes mellitus is an increasing health problem in many countries. In 2006, the WHO estimated that 180 million people worldwide had diabetes, and that this number will likely be more than doubled by 2030. The number of deaths attributable to diabetes has been estimated at 2.9 million per year.^[1] Type 1 diabetes mellitus (T1DM) is characterized by an inability of the body to produce insulin, and has to be treated with exogenous insulin. Type 2 diabetes mellitus (T2DM) reflects both insulin resistance of liver and peripheral tissues, and deficient insulin secretion by pancreatic β -cells.^[2] Various oral antidiabetic drugs, as well as insulin, are used for treatment. The factors contributing to the pathophysiology and disease progression of diabetes are not yet fully understood. Long-term complications such as neuropathy, nephropathy and retinopathy are debilitating for patients and result in high healthcare costs. In the US, diabetes was the leading cause of renal failure and new blindness in 2005,^[3] and total diabetes costs were estimated at \$US174 billion in 2007.^[4]

For these reasons, early diagnosis and adequate treatment are important to decrease the long-term adverse effects of diabetes. Mathematical models are needed to better understand the glucose-insulin system, to evaluate diagnostic tests, to study and predict drug effects, and to quantify disease progression. Mechanism-based models are preferable, as they can be used to study the mechanism of action and to predict the effects of new dosage regimens. If the number of time- and cost-intensive long-term clinical trials that need to be performed can be reduced by simulation studies, the time and costs involved in drug development could be considerably decreased, and optimized dosage regimens could be prospectively designed and clinically evaluated. Pharmacokinetic/pharmacodynamic modelling can also help to design better studies, to identify agents with undesirable properties earlier and to decrease attrition rates at late stages of drug development.^[5]

Since the 1960s, numerous interesting and useful mathematical models have been developed for various applications and with different characteristics and employing different methods. With this large number of models, it is sometimes difficult to decide which one should be used for a specific purpose. A few reviews are available on certain aspects of diabetes modelling.^[6-10] However, no extensive overview has been published that includes the different types of pharmacodynamic models and assesses the mechanisms of drug effects. This review summarizes the state-of-the-art in diabetes modelling, with a focus on models describing drug effects. We sought to identify major strengths and limitations of the published models and further needs and perspectives in diabetes modelling.

We performed a literature search of MEDLINE, EMBASE, the references of published papers and abstracts from various conferences. The models were subcategorized as models for (i) diagnostic tests; (ii) intrinsic interactions of glucose and insulin; (iii) antidiabetic drug effects; (iv) secondary drug effects; (v) ancillary

biomarkers; and (vi) disease progression. This review focuses on models for system and parameter estimation and includes some simulation models.

1. The Glucose-Insulin System

Diabetes is a multiorgan disease, which is mainly characterized by a disturbance of glucose-insulin homeostasis. A simplified diagram of the regulation of the glucose system by insulin and other endogenous substances is shown in figure 1. The diagram describes the action of relevant biomarkers by stimulation or inhibition of production or utilization of other endogenous substances. The plasma glucose concentration is increased by hepatic glucose production and absorption from the gut after food intake. It decreases due to utilization by the brain and peripheral tissues such as muscle and fat. One of the key characteristics of the glucose-insulin system is reciprocal feedback between glucose and insulin, i.e. an increase in glucose concentrations stimulates production of insulin, and insulin in turn stimulates utilization of glucose and inhibits production of glucose.

In general, the human body aims to maintain blood glucose concentrations within a narrow range of about 80–115 mg/dL.^[2] For example, tissues such as the brain and erythrocytes need a constant supply of glucose. Therefore, in the fasting state, glucose is produced by breakdown of glycogen (glycogenolysis) in the liver. After an extended fasting period, hepatic glycogen stores are depleted. Then glucose is produced mainly from gluconeogenesis in the liver (and to a small extent in the kidneys), utilizing mainly amino acids from muscle tissue, lactate or glycerol. Both glycogenolysis and gluconeogenesis are stimulated by glucagon, a peptide hormone that is secreted from pancreatic α -cells at low blood glucose concentrations (figure 1). Only a low basal insulin secretion occurs at glucose concentrations below about 80 mg/dL.^[14] In the fasting state, most of the glucose is taken up by insulin-independent tissues such as the brain, and <20% is taken up by the muscle.^[15] During strenuous exercise and anaerobic conditions, glycogen in muscle tissue is broken down to lactate, which is released into the blood and taken up by the liver, where it can be stored as glycogen or converted into glucose by gluconeogenesis. The concept of resynthesis of glucose from lactate in the liver was formulated by Cori and is known as the Cori cycle or the glucose-lactate cycle.^[16] The Cori cycle includes the breakdown of glucose to lactate in muscle tissue via anaerobic glycolysis, uptake of lactate into the liver, conversion of lactate to glucose in the liver, and uptake of glucose into muscle tissue again.

After a meal is ingested, complex carbohydrates from the food are split into oligosaccharides which, in turn, are broken down to monosaccharides such as glucose by α -glucosidases in the gut wall (figure 1). Glucose is absorbed into the blood, and glucose concentrations increase. Due to increasing glucose concentrations, secretion of insulin from pancreatic β -cells is stimulated (figure 1).

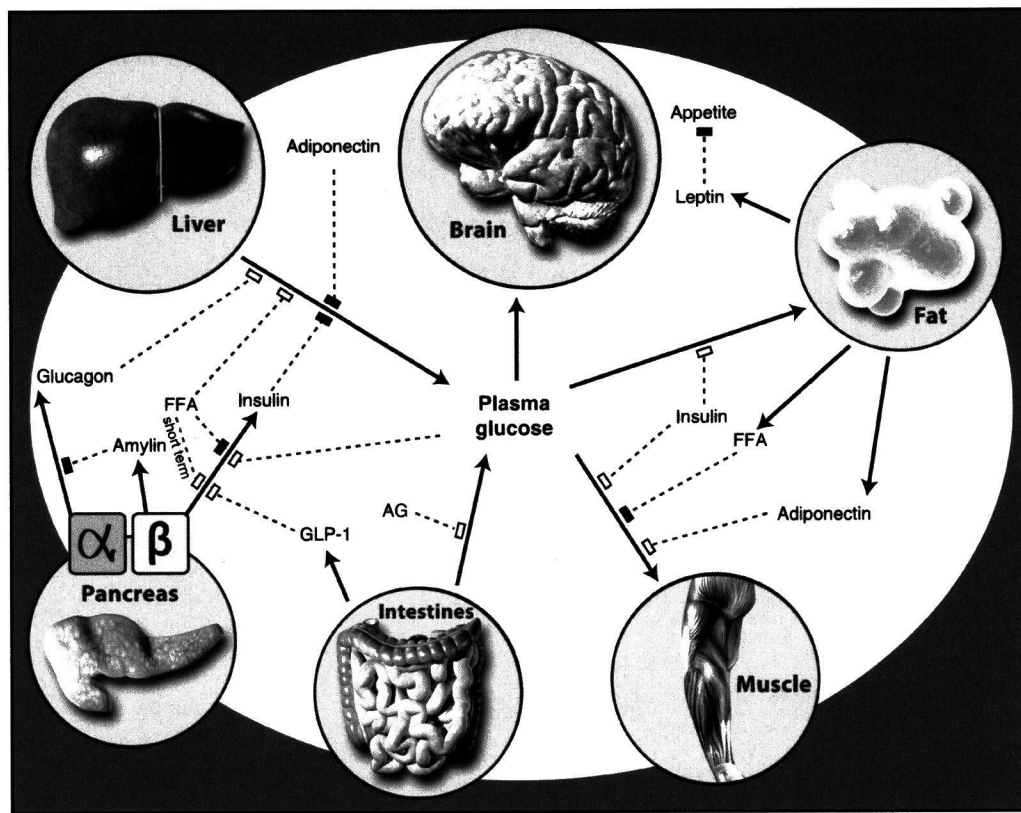


Fig. 1. Simplified diagram of the regulation of glucose metabolism,^[11-13] describing the action of relevant biomarkers by stimulation (open bars) or inhibition (solid bars) of production/utilization of other endogenous substances. Many more biomarkers are involved in glucose regulation but have been omitted from this diagram for clarity. **AG** = α -glucosidases; **FFA** = free fatty acids; **GLP-1** = glucagon-like peptide 1.

At increased blood glucose concentrations, more glucose is taken up into β -cells and metabolized to adenosine triphosphate, which results in closure of potassium channels, membrane depolarization, opening of calcium channels, an increase in intracellular calcium concentrations and, eventually, increased insulin secretion.^[11]

Insulin is secreted in equimolar amounts with C-peptide (connecting peptide) from β -cells. C-peptide is formed due to cleavage of insulin from pro-insulin. As a large and variable proportion of the secreted insulin is metabolized during the first pass through the liver, and C-peptide is not extracted by the liver, peripheral C-peptide concentrations are often measured to study insulin secretion.^[17]

In the short-term, insulin secretion is stimulated by high concentrations of glucose, free fatty acids (FFA)^[18,19] (figure 1) and amino acids.^[20] However, long-term exposure to elevated concentrations of FFA (lipotoxicity)^[19,21] (figure 1), glucose (glucotoxicity)^[21] or amino acids^[20] results in β -cell failure and decreased insulin secretion. Insulin secretion is also stimulated by incretin hormones, such as glucagon-like peptide 1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP), which are secreted

from the gut wall after food intake (see later in this section and in figure 1).

As shown in figure 1, insulin inhibits hepatic glucose production and stimulates glucose utilization by peripheral tissues. Insulin promotes uptake of glucose and storage as glycogen in the liver and skeletal muscle. It also enhances glucose disposal by stimulation of glycolysis in muscle tissue. Liver glycogen is a readily available glucose reservoir for the maintenance of blood glucose concentrations in the fasting state, whereas muscle glycogen is used to store energy for the muscle itself. Glucose uptake by the brain is insulin-independent, as the brain cannot store glucose and therefore needs a permanent supply of energy (as shown in figure 1, where there is no stimulation of brain glucose uptake by insulin). At a high carbohydrate intake, insulin also stimulates conversion of glucose to fatty acids and their uptake into adipose tissue, where they are stored as triglycerides. Insulin also stimulates uptake of amino acids and their storage as protein in skeletal muscle, and uptake of FFA and their storage as triglycerides in adipose tissue. In addition, insulin inhibits hepatic gluconeogenesis by inhibition of key enzymes of this pathway, including phosphoenolpyruvate carboxykinase (PEPCK), which catalyses the rate-limiting step of gluconeogenesis and also inhibits hepatic

glycogenolysis (figure 1). Insulin also inhibits the release of amino acids from skeletal muscle and the release of FFA and triglycerides from adipose tissue.

These insulin actions lead to a decrease in blood glucose concentrations and promote storage of energy in the tissues (anabolic action). Glucagon, conversely, stimulates the release of glucose, FFA and amino acids from the liver, fat and muscle (catabolic action). At high blood glucose concentrations, secretion of insulin is stimulated while glucagon secretion is inhibited, and vice versa at low blood glucose concentrations.

T1DM patients have an absolute deficiency of insulin, whereas T2DM is characterized by impaired insulin secretion and resistance to insulin action in the liver and peripheral tissues. T1DM and T2DM patients who require insulin therapy have elevated postprandial glucagon concentrations,^[22] whereas T1DM patients also have fasting hyperglycaemia. In addition, it has been proposed that reduced suppression of glucagon secretion by insulin contributes to impaired glucose tolerance.^[23] Insulin deficiency and glucagon excess lead to decreased glucose uptake into cells, increased breakdown of protein and lipolysis. In severe uncontrolled diabetes, the release of large amounts of FFA that are converted to ketone bodies in the liver can result in ketoacidosis.

Amylin is co-secreted with insulin from β -cells. It is a hormone that has been shown to inhibit postprandial glucagon secretion^[24] (figure 1). Amylin also acts by delaying gastric emptying and reducing food intake.^[22] Therefore, amylin promotes the decrease of high postprandial blood glucose concentrations. Amylin secretion is lacking in T1DM patients and impaired in T2DM patients because of depletion or dysfunction of β -cells.^[22,25] In rodents, especially in the fasting state, injection of amylin resulted in increased concentrations of lactate due to enhanced muscle glycogen breakdown. Subsequently, glucose concentrations increased, as lactate is a substrate for gluconeogenesis in the liver.^[26,27] Increased concentrations of lactate in human muscle, adipose tissue and plasma, due to lactate release from muscle and adipose tissue, have been shown after glucose ingestion.^[28]

After enteral nutrition, the incretin hormones GLP-1 and GIP are secreted from cells in the gut wall (figure 1). The secretion is stimulated by endocrine and neural signals and by direct stimulation of the intestinal cells by digested nutrients. Both GLP-1 and GIP stimulate glucose-dependent insulin secretion from β -cells (figure 1), enhance β -cell proliferation and increase β -cell resistance to apoptosis. In addition, GLP-1 inhibits glucagon secretion, slows down gastric emptying and food ingestion, and decreases food intake.^[29,30] Therefore, GLP-1 and GIP both act to decrease high blood glucose concentrations after food intake. Both GLP-1 and GIP are rapidly inactivated by the ubiquitous enzyme dipeptidylpeptidase-4 (DPP-4). The half-life of active GLP-1 in plasma is <2 minutes.^[30] The active GIP half-life has been reported to be 7 minutes in healthy subjects and 5 minutes in T2DM pa-

tients.^[30,31] Reduced secretion of GLP-1 and decreased action of GIP in T2DM patients compared with healthy subjects has been reported.^[29]

FFA play an important role in glucose metabolism. FFA are important for β -cell function and stimulate insulin secretion.^[18] However, permanently increased FFA concentrations cause 'lipotoxicity' and decrease insulin secretion from β -cells (figure 1). Obesity, especially an increased mass of visceral fat, leads to increased concentrations of FFA, as visceral fat exhibits higher lipolytic activity than subcutaneous fat. Increased concentrations of FFA stimulate hepatic gluconeogenesis^[32] and decrease glucose uptake into skeletal muscle (figure 1). Permanently increased FFA concentrations promote insulin resistance in both skeletal muscle and the liver. As skeletal muscle is responsible for about 75–80% of insulin-mediated glucose disposal, decreased glucose uptake by the muscle due to peripheral insulin resistance can substantially increase plasma glucose concentrations.^[33–35] In 1963, Randle et al.^[36] proposed the glucose-fatty acid cycle, according to which fuel selection from FFA is preferred over glucose. Therefore, increased availability of FFA results in decreased glucose uptake into muscle cells. More recently, it was reported that FFA also induce or enhance insulin resistance due to alterations in insulin signalling,^[37] which leads to decreased muscle glucose transport, possibly due to diminished glucose transporter protein isoform 4 (GLUT-4) translocation.^[38] GLUT-4 is the major insulin-sensitive glucose transporter in adipose tissue and muscle, and facilitates glucose uptake into these tissues.^[39] In obese and T2DM patients, lipolysis is increased, as the adipose tissue is insulin resistant, therefore plasma FFA concentrations are higher which, in turn, aggravates insulin resistance in the liver and skeletal muscle, and causes deterioration of β -cell function.

Recently, it was recognized that adipose tissue is not only a storage tissue but has endocrine functions and secretes hormones (adipokines) such as adiponectin and leptin (figure 1). Adiponectin, which is specifically secreted from adipose tissue, stimulates glucose uptake and utilization in skeletal muscle and inhibits gluconeogenesis in the liver (figure 1). Therefore it supports insulin action, increases insulin sensitivity and decreases plasma glucose concentrations. Reduced adiponectin concentrations have been related to a higher incidence of diabetes, insulin resistance, cardiovascular disease and metabolic syndrome.^[40,41]

Leptin, which is produced primarily by adipose tissue, acts as a central satiety signal (figure 1). Leptin decreases food intake, stimulates energy expenditure and increases insulin sensitivity. Leptin- or leptin receptor-deficient animal models exhibit obesity and insulin resistance. Obese subjects have higher leptin concentrations because they have a larger fat mass than lean subjects. However, obesity appears as a condition of relative leptin resistance, and therefore the effect of leptin is decreased.^[41,42]

A simplified diagram, such as in figure 1, can be useful for model building. Depending on the observed data and the most relevant subsystem (e.g. for the action of a drug), part of this diagram can be used as the starting point for a model. To date, most mathematical models have focused on glucose, insulin or both, and have not included other biomarkers.

2. Mechanisms of Action of Antidiabetic Drugs

T1DM patients cannot produce insulin, and therefore their treatment mainly consists of exogenous insulin. Numerous therapeutic options are available for T2DM. An overview of the mechanisms and sites of action for the different groups of antidiabetic drugs is shown in figure 2.

Hyperglycaemia in T2DM patients can, among other reasons, be due to the following: (i) decreased uptake of glucose into skeletal muscle due to peripheral insulin resistance; (ii) increased hepatic glucose production (mainly gluconeogenesis) due to hepatic insulin resistance; and (iii) decreased insulin secretion due to exhaustion of β -cells, genetic causes, lipotoxicity or glucotoxicity.^[2,43] Therefore, drugs that ameliorate one or more of these defects can be used in treating T2DM. It is generally assumed that

insulin resistance precedes β -cell failure in T2DM.^[2,15] However, there is also evidence for the theory that β -cell dysfunction is present before insulin resistance.^[44] In general, as long as the β -cells can increase insulin production enough to compensate for an enhanced need due to insulin resistance, the patients do not become hyperglycaemic.^[2,44] However, loss of β -cell function, most likely due to accelerated apoptosis,^[44] leads to overt diabetes. Therefore, it has been suggested that approaches that delay the loss of β -cell function, e.g. by decreasing glucotoxicity and lipotoxicity, which are reversible, should be considered.^[12]

Sulfonylurea drugs stimulate insulin secretion from β -cells. Through binding of the drug to receptors on the β -cells, potassium channels are closed, which results in stimulation of insulin secretion by a mechanism similar to stimulation of insulin secretion by glucose, as described in section 1. Examples of sulfonylurea drugs for which models have been proposed are glimepiride, gliclazide, tolbutamide and glibenclamide (glyburide). Meglitinides such as repaglinide and nateglinide stimulate insulin secretion by the same mechanism as sulfonylureas but have a faster onset and a shorter duration of action.^[11]

Metformin is one of the biguanides. It is reported to suppress gluconeogenesis and glycogenolysis, increase insulin-mediated

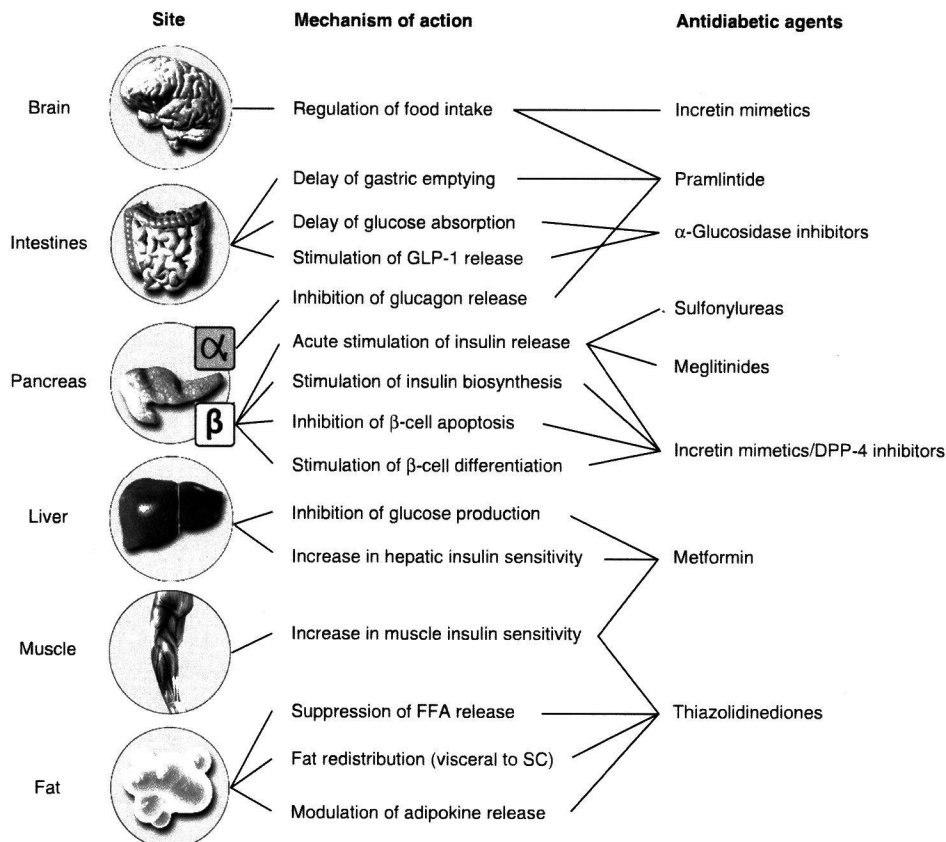


Fig. 2. Sites and mechanisms of action of antidiabetic agents (adapted from Stumvoll et al.,^[15] with permission from Elsevier). **DPP-4** = dipeptidylpeptidase-4; **FFA** = free fatty acids; **GLP-1** = glucagon-like peptide 1; **SC** = subcutaneous.

glucose uptake into muscle and adipose tissue, and stimulate anaerobic glucose metabolism in the intestine. Metformin is sometimes called an insulin sensitizer, as it increases hepatic and peripheral insulin sensitivity.^[11]

Thiazolidinediones such as rosiglitazone and pioglitazone act by stimulation of nuclear peroxisome proliferator-activated receptor γ (PPAR γ), which affects the transcription of genes that regulate glucose and lipid metabolism. Stimulation of PPAR γ increases glucose uptake by the GLUT-4 transporter in muscle and adipose tissue by improving translocation of GLUT-4 to the cell surface. Stimulation of PPAR γ also decreases concentrations of FFA, which results in enhanced glucose utilization, decreased gluconeogenesis and increased muscle insulin sensitivity. In addition, PPAR γ agonists stimulate secretion of adiponectin and inhibit secretion of tumour necrosis factor (TNF)- α from fat cells, affect the secretion of other adipokines, and promote redistribution of fat from visceral to subcutaneous fat, which has lower lipolytic activity. Thiazolidinediones are also often called insulin sensitizers and have been reported to partially reverse insulin resistance.^[45] In addition, they improve fasting plasma glucose (FPG) levels, mainly by inhibition of gluconeogenesis.^[46]

Acarbose and miglitol are α -glucosidase inhibitors, which slow down the breakdown of poly- and oligosaccharides to monosaccharides, such as glucose, and delay glucose absorption from the intestines. Glucose is absorbed from more distant regions of the gut, which results in increased stimulation of GLP-1 production.^[15] α -Glucosidase inhibitors are not absorbed into the systemic circulation.

Pramlintide is an amylin analogue and amylin receptor agonist. It retains the biological activity of amylin but, in contrast to amylin, it does not aggregate into amyloid plaques, which are deposited in β -cells. Amyloid plaques may be linked to β -cell dysfunction^[15] and development of T2DM.^[25] Pramlintide is used as an adjunct to mealtime insulin in T1DM and T2DM patients. Like amylin, pramlintide decreases postprandial secretion of glucagon, delays gastric emptying and increases satiety,^[22,47] all leading to decreased glucose excursions after a meal.

Incretin mimetics are GLP-1 receptor agonists that are not inactivated by DPP-4 and have a longer duration of action than GLP-1. Like GLP-1, they stimulate glucose-dependent insulin release, stimulate insulin biosynthesis and β -cell differentiation, inhibit β -cell apoptosis and enhance satiety.^[29] Examples are exenatide (synthetic exendin-4), which is approved in the US and the EU, and liraglutide, which is in the late stages of clinical development.

DPP-4 inhibitors prolong the action of GLP-1 by inhibiting its inactivation by DPP-4. They have similar effects to those of the incretin mimetics but do not seem to influence food intake.^[29] Sitagliptin is on the market in the US and the EU. Vildagliptin is approved in Europe.

Overall, as diabetes is a multiorgan disease, drugs with different sites and mechanisms of action are used. Furthermore, one drug can have more than one site or mechanism of action. If a model includes these different mechanisms for one drug, the action of a drug can potentially be better described and predicted. However, more data and more complex models are usually needed.

3. Overview of Diabetes Mellitus Models

Most of the earlier models focused on description of the glucose-insulin system and evaluation of diagnostic tests (table I). In 1980, Berman^[48] published an overview of models for insulin kinetics. Models published during the 1960s and 70s have been divided into two categories:^[49] (i) 'simple' models with a minimum number of parameters, such as the pioneer model published by Bolie in 1961;^[50] and (ii) comprehensive 'library' models,^[51-53] which aim to describe the system as extensively as possible. For the latter, not all parameters can be estimated.^[49] Two models for diagnostic purposes that were originally published in 1979 and are still widely used are the minimal model^[54] and homeostatic model assessment (HOMA).^[55]

Overall, a large number of models have been developed. Table II lists various purposes for which models have been published. Models for estimation tend to have fewer parameters to retain parameter estimability. They are most often used to estimate pharmacokinetic/pharmacodynamic parameters after diagnostic tests or administration of antidiabetic drugs, and to quantify disease progression. Models for simulation are usually large, too complex to allow estimation, and aim to describe the physiological situation as closely as possible for certain organs or tissues or even the whole body. Whole-body simulation models may be used to perform virtual trials, which are difficult to perform in real human subjects for ethical or practical reasons.

Table I. Early models of the glucose-insulin system

Year	Development	References
1939	First approach to measure insulin sensitivity <i>in vivo</i>	56
1959	Steele's equations for glucose (dis)appearance	57
1961	Bolie pioneer model for glucose-insulin system	50
1965	Model similar to Bolie's fitted to data from OGTT	58
1966	Glucose clamp technique introduced	59,60
1970-5	More comprehensive 'library' models	51-53
1979	Original 'minimal model'	54
1979	Original HOMA model	55

HOMA = homeostatic model assessment; OGTT = oral glucose tolerance test.

Table II. Array and purposes of developed models

Model and purpose	Estimation	Simulation only
Diagnostics: insulin sensitivity and pancreatic β -cell function	✓	
Glucose-insulin system after tolerance tests	✓	
Glucose-insulin system in the physiological situation	✓	✓
Important subsystems		
β -cell dynamics	✓	✓
insulin binding to receptors	✓	
oscillations in insulin secretion		✓
glycosylation of haemoglobin	✓	✓
fuel selection in muscle tissue		✓
insulin signalling		✓
translocation of GLUT-4		✓
Effects of antidiabetic drugs	✓	
Secondary drug effects	✓	
Ancillary biomarkers	✓	✓
Disease progression	✓	✓
Whole-body simulations (including drug effects)		✓

GLUT-4 = glucose transporter protein isoenzyme 4.

4. Models for the Intrinsic Interaction Between Glucose and Insulin

4.1 Models for Diagnostic Tests

To establish if a person is diabetic or likely to become diabetic, various diagnostic tests have been developed. The goal of these experiments is to obtain an estimate of β -cell function, insulin sensitivity (most often) or both. Therefore, the clinical utility of the models that may be applied to analyse data from the diagnostic tests described below is to indicate the diabetic or prediabetic state of a patient. Several methods for estimation of β -cell function were compared by Kjems et al.^[17,61] Overviews of methods to determine insulin sensitivity were published by Monzillo and Hamdy^[62] and Wallace and Matthews.^[63] The two methods for determination of insulin sensitivity that are considered as 'gold-standard' by the American Diabetes Association (ADA) are the hyperinsulinaemic euglycaemic clamp and the intravenous glucose tolerance test (IVGTT). For the euglycaemic clamp, generally a constant rate insulin infusion is given, which results in insulin concentrations above the physiological baseline. Blood glucose is measured frequently and maintained within the euglycaemic range by a glucose infusion with adjusted rates. As hepatic glucose production is assumed to be completely inhibited by exogenous insulin infusion, the glucose infusion rate (GIR) equals the glucose utilization rate and reflects the insulin sensitivity of the peripheral tissues. Although some authors have applied or developed models

for glucose clamp data,^[64-68] in the majority of studies, no modelling was performed for evaluation of the experimental data.

For the IVGTT, a glucose bolus of 0.3 g/kg of bodyweight is administered, and plasma glucose and insulin are measured at 12–30 timepoints over 3 hours after the dose.^[62] The minimal model was developed by Bergman et al.^[49,54,69,70] to estimate insulin sensitivity and glucose effectiveness after an IVGTT. The intention was to find a model that could capture the most important physiological features of the glucose-insulin system and allow estimation of key parameters. The minimal model provides an estimate of insulin sensitivity without the need to perform the experimentally more complex glucose clamp method. The minimal model was developed from experiments in five dogs. Seven different models were compared using data from nine experiments in two dogs receiving an intravenous glucose bolus. The best model was selected based on comparison of model fits and meaningfulness of parameter estimates.^[54] Figure 3 shows the compartmental structure and the equations for the minimal model, including parameter explanations. Use of the minimal model has been reported in more than 500 papers,^[71] with about 50 published each year.^[69] Despite this extensive use, several authors have pointed out limitations of the minimal model.^[6,8,72-74] The interpretation of the unobserved insulin effect compartment [$X(t)$, unit: min^{-1}] is controversial. In 2005, Bergman^[69] stated that $X(t)$ is proportional to insulin in the interstitial fluid and that the model assumes that the delay in insulin action is due to the time necessary for insulin distribution to the interstitial fluid. Based on this explanation for the delay in insulin action and *in vivo* experiments, Bergman^[75] proposed a 'single gateway hypothesis': insulin has to diffuse into interstitial fluid in muscle and adipose tissue in order to affect peripheral glucose utilization and hepatic glucose production. Another interpretation of $X(t)$ could be as a signal transduction compartment. Some authors have identified the representation of the glucose system by a single compartment as a limitation of the minimal model that can affect the precision and accuracy of parameter estimates.^[9,73] Another concern is that glucose and insulin are estimated separately and therefore there is insufficient interaction, as the mutual feedback is not taken into account.

In the minimal model of glucose disappearance (figure 3), the insulin concentration is considered as an independent variable that is known without error. A function that interpolates between the measured insulin concentrations is needed as the driving force for estimation of the glucose parameters. For estimation of plasma insulin concentrations (figure 3), measured glucose concentrations are used as an independent variable. De Gaetano and Arino^[74] provided a mathematical evaluation of the minimal model. They combined the two parts of the model to estimate glucose and insulin simultaneously, and subsequently showed that for commonly observed parameter values, this would lead to an infinite increase of insulin in the remote compartment [$X(t)$]. After a

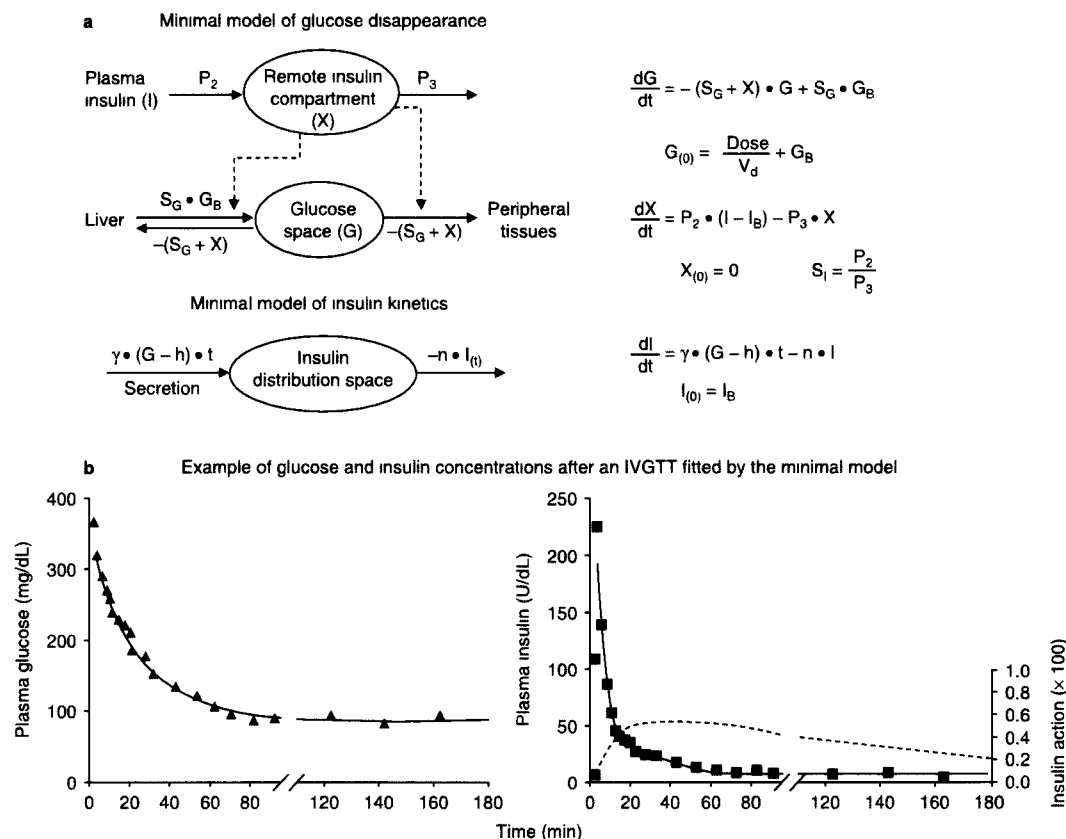


Fig. 3. Compartmental structure and equations of the minimal model^[49,54,76] (adapted from Bergman et al.^[77] with permission). γ = rate of pancreatic release of insulin per min and per mg/dL of glucose concentration above the target glycaemia ($\mu\text{U} \cdot \text{mL}^{-1} \cdot \text{min}^{-2} \cdot \text{dL} \cdot \text{mg}^{-1}$); G = blood glucose concentration (mg/dL); $G_{(0)}$ = G at time $t = 0$; G_B = baseline blood glucose concentration (mg/dL); h = pancreatic target glycaemia (mg/dL), $(G - h)$ set to 0 if $G < h$; I = insulin concentration in plasma ($\mu\text{U}/\text{mL}$); $I_{(0)}$ = I at time $t = 0$; I_B = basal insulin concentration at the end of the test ($\mu\text{U}/\text{mL}$); $I(t)$ = I at time t ; **IVGTT** = intravenous glucose tolerance test; n = first-order decay rate constant for insulin in plasma (min^{-1}); P_2 = fractional rate of insulin appearance in interstitial fluid ($\text{min}^{-2} \cdot \mu\text{U}^{-1} \cdot \text{mL}$); P_3 = 'fractional clearance' (first-order rate constant) of insulin from the interstitial compartment (min^{-1}); S_G = glucose effectiveness (min^{-1}) and describes tissue uptake of glucose at basal insulin concentrations; S_1 = insulin sensitivity index ($\text{min}^{-1} \cdot \mu\text{U}^{-1} \cdot \text{mL}$), describes hepatic and peripheral insulin sensitivity, and is a composite measure of stability of remote insulin and glucose sensitivity to insulin; t = time after drug administration; V_d = volume of distribution; X = 'insulin action' in remote compartment (interstitial fluid, unit of X : min^{-1}); $X_{(0)}$ = X at time $t = 0$.

formal analysis of the coupled model, they concluded that it is mathematically incorrect.^[74] For instance, if the target glucose concentration is lower than baseline, steady state cannot be reached, and insulin in the remote compartment increases infinitely.^[74]

In diabetic patients or for an IVGTT with a reduced number of samples, parameter estimation can be difficult. In severe insulin resistance, the minimal model often yields negative values for insulin sensitivity (figure 3) unless an adequate dose of exogenous insulin is given after the glucose bolus (modified IVGTT).^[73]

The model also assumes a linear rise in insulin secretion, with a constantly elevated glucose concentration. The uncommon parameter units lead to controversy about the interpretation of the parameters. However, the model is appropriate for application in clinical practice and epidemiological studies, has a limited number

of estimable parameters and is available as a commercial program. These factors are likely reasons for its appreciable use.

Numerous extensions and variants of the minimal model have been published, and a list is given in table III. Mari^[9] published an overview of the minimal model and its extensions. Although the model has been developed specifically for the IVGTT, modifications have been made to also apply the model to the oral glucose tolerance test (OGTT) and meal tests.^[9] The minimal model has been successful for analysis of data from diagnostic tests. However, its applicability to situations outside this arena seems limited.

Another method that is often employed for diagnostic purposes is HOMA.^[55,87] More than 500 papers using HOMA have been published.^[88] HOMA is a physiologically based 'paradigm model' that includes a feedback loop between hepatic glucose output and insulin secretion by β -cells as the central element. In the model, the plasma glucose concentration is regulated by insulin-depen-

dent hepatic glucose output, and the insulin concentration depends on the β -cell response to glucose. Glucose uptake in fat and muscle is dependent on glucose and insulin concentrations, whereas glucose uptake into the brain and kidneys depends only on the glucose concentration. Application of the model does not involve curve fitting. The predictions from the model are based on experimental data on β -cell, hepatic and peripheral responses in humans and animals. For example, the β -cell insulin secretion curve is based on near-steady-state C-peptide responses to hyperglycaemic clamps in a study done in six healthy subjects.^[87] An approximated theoretical solution adjusted to population norms for the parameters based on human and animal data is available (HOMA1). It requires a patient's FPG and fasting plasma insulin (FPI) concentrations on one occasion to be entered in equations (equations 1 and 2).^[87-89]

$$\text{HOMA1-\%S} = \frac{22.5}{\text{FPG} \cdot \text{FPI}} \tag{Eq. 1}$$

$$\text{HOMA1-\%B} = \frac{20 \cdot \text{FPI}}{(\text{FPG} - 3.5)} \tag{Eq. 2}$$

The patient's β -cell function (HOMA1-%B) and insulin sensitivity (HOMA1-%S, assuming equivalent peripheral and hepatic insulin sensitivity), compared with 'normal' function, can be calculated. Sometimes HOMA-IR is reported as a measure of insulin resistance, and it is the reciprocal of HOMA-%S. HOMA is considerably more convenient and easier to perform than an IVGTT, and is applicable for use in epidemiological trials. HOMA1 is a mathematical approximation of the original non-linear model and has been reported to work well for assessing relative change, e.g. disease progression within individuals.^[88] HOMA2 is the exact solution of the model. An online calculator, where β -cell function and insulin sensitivity can be derived from the exact solution of the model, is available. Use of the exact solution is recommended for comparison of the results with other models or assessment of absolute insulin sensitivity or β -cell function.^[88,89] However, the full set of equations for the model does not appear to have been published. A review of the HOMA model has been published by Wallace et al.^[88] The authors point out that the model has not yet been validated for patients on treatment with insulin or secretagogues, or for animals, and that it has limited use in severe diabetes.^[88] Limited applicability of the HOMA model in elderly patients has been reported.^[90]

Recently, more complex semimechanistic models for evaluation of diagnostic tests have been proposed. De Gaetano and Arino^[74] aimed to address the limitations of the minimal model and suggested a so-called 'dynamical model' employing delay differential equations. Their model can be used to estimate glucose and insulin simultaneously and takes into account the feedback relationship. According to the authors, it can also be used for data

other than from IVGTT.^[74] Good curve fits to glucose and insulin concentrations were shown; however, only profiles from three subjects were included. A critical evaluation and a generalized version of this model were published by Li et al.^[91]

Most recently, Silber et al.^[92] published a population model for glucose and insulin regulation and used the model proposed by De Gaetano and Arino^[74] as a starting point. They had data from different studies, including IVGTT with radiolabelled glucose with or without insulin in healthy subjects, IVGTT with radiolabelled glucose in diabetic subjects and a euglycaemic clamp study in healthy subjects. The advantages of this model were that glucose and insulin were modelled simultaneously and that the model included feedback in both directions (glucose stimulates second-phase insulin secretion, and insulin stimulates elimination of glucose).

Glucose was described by a two-compartment disposition model with both insulin-independent and insulin-dependent elimination. A negative feedback of glucose on its own production was included. The authors reported that their modelling suggested that the effect of insulin on glucose production was negligible. The delay in the feedbacks was described by use of three effect compartments. The first-phase insulin secretion was modelled as a bolus dose. Both insulin-dependent and insulin-independent glucose clearance were only one-third in patients compared with healthy subjects. In patients, first-phase insulin secretion and the feedback control on endogenous glucose production was estimated to be close to zero. Whereas endogenous glucose production was expected to be higher in patients than in healthy subjects,^[92] the model suggested that it was similar in the two groups. According to the authors, one reason might be lack of information in the

Table III. Extended minimal models^a

Extensions and variants of minimal model	References
C-peptide model to assess pancreatic insulin secretion	78-80
OGTT, mixed meal tests (including fat)	9
Free fatty acids	81
T1DM patients, effect of food, renal glucose clearance	82
Physical exercise	83
Separate insulin effect on glucose production and utilization (labelled 'hot' glucose)	84
Two compartments for glucose disposition identified by a Bayesian approach	85
Separate effects of insulin on glucose production, distribution, transport and utilization	86
Joint model for simultaneous estimation of glucose and insulin that is not necessarily associated with IVGTT	74 ^b

a See also the review article by Mari.^[9]

b Including formal mathematical analysis of the minimal model.

IVGTT = intravenous glucose tolerance test; **OGTT** = oral glucose tolerance test; **T1DM** = type 1 diabetes mellitus.

patient data. The model showed a reasonably good predictive performance, especially considering that data from different studies were modelled simultaneously.

An extension of the model, which can be applied to OGTTs, was published recently.^[93,94] Lately, in a presentation by Dansirikul and Karlsson,^[95] incorporation of C-peptide kinetics into the previously developed model was shown.

Gupta et al.^[96,97] developed a model that included the kinetics of insulin inside β -cells and has the advantage of being based on physiological processes. The aims were to differentiate between the pancreatic responsiveness in lean and obese children, and to detect an existing prediabetic condition in first-phase insulin secretion. Plasma glucose and insulin were measured in six obese and six lean children between 8 and 12 years of age during an IVGTT. Plasma glucose was interpolated by a spline function and entered into the model as an independent variable that was assumed to be known without error. The ability to identify prediabetic subjects would be valuable. However, simulations from the model performed by us showed no first-phase insulin secretion. The importance of first-phase insulin secretion is still controversial.^[98] To apply and assess this model, it would be helpful to know how the parameters for processes inside β -cells were estimated from plasma glucose and insulin measurements, or if they were taken from the literature or *in vitro* experiments.

A model including three feedback pathways (glucose stimulates production of insulin, insulin stimulates utilization of glucose, and insulin inhibits production of glucose) has been developed and applied to data from a euglycaemic clamp study.^[65] The model employs stochastic differential equations to distinguish between random variations in glucose metabolism and measurement error. Therefore, variations in glucose concentrations could be captured, whereas glucose concentrations and disposition are usually assumed to be constant during clamp studies. Another example in which the fluctuations of glucose concentrations during a glucose clamp were modelled is discussed in section 5.2.^[66]

The prehepatic insulin secretion rate (ISR) may be estimated by analysing peripheral C-peptide concentrations, as C-peptide and insulin are secreted in equimolar amounts and C-peptide is not extracted by the liver (see section 1).^[17] A common method of estimating the ISR is the deconvolution method, which is a 2-day method as it requires separate assessment of C-peptide kinetics after a dose of exogenous C-peptide.^[78,99] With this method, C-peptide is usually modelled by a two-compartment disposition model. Volund et al.^[100] developed and introduced a method for estimation of insulin secretion from a single experiment. Insulin and C-peptide were infused intraportally into dogs, with a changing rate of infusion, while endogenous insulin and C-peptide release were suppressed with somatostatin. Glucose was clamped at the basal concentration during this procedure. Measured plasma

insulin and C-peptide were modelled simultaneously by one disposition compartment for each peptide. The infusion rate for both peptides and the fraction of insulin eliminated during the first pass through the liver were estimated. The model was validated by comparison of the known and estimated infusion rates and calculation of the correlation between both. The authors concluded that a one-compartment model for both peptides is an acceptable approximation.

Subsequently, Watanabe et al.^[101] applied the method from Volund et al.^[100] to data from IVGTTs in healthy women and estimated prehepatic first- and second-phase insulin secretion. The percent hepatic extraction of insulin was estimated at 54%. Average model fits were shown. Christiansen et al.^[102] compared the deconvolution method with the combined model using data from pancreas-kidney transplant patients during slow (OGTT) and fast (intravenous glucagon) changes in insulin secretion. They concluded that the combined model may give sufficiently accurate results with slow changes in insulin secretion. In general, analysis of the individual C-peptide kinetics is suggested in pancreas-kidney transplant patients. As T2DM is characterized by a decrease in the ISR, the clinical utility of models that estimate the ISR is that the impact of different pathophysiologies or, for example, pancreas transplants on insulin secretion can be explored.

Further models for diagnostic tests, especially those including C-peptide kinetics and models describing the process of insulin secretion, were reviewed in 1994 by Pacini.^[10]

Overall, the well established minimal model and HOMA are frequently used, possibly because they have easy applicability in the clinic. Recently, however, more mechanistic models have been developed, with the goal being to improve early diagnosis of diabetes or prediabetes and to provide further insights into the glucose-insulin system.

4.2 Models for the Glucose-Insulin System Not Intended for Diagnostic Tests

A central characteristic of the glucose-insulin system is the reciprocal feedback relationship, i.e. glucose stimulates production of insulin, and insulin stimulates utilization of glucose, inhibits production of glucose, or both (see figure 1 and section 1). This represents a challenge to fitting, owing to circular behaviours, and most models do not include the feedback. A way to incorporate the feedback in a physiologically mechanistic way without the need to add a large number of additional parameters was shown by Lima et al.^[103] A similar approach had been taken by Ackerman et al.^[58] in 1965 when they fitted a model similar to the Bolie pioneer model,^[50] a system of two linear differential equations, to data from OGTTs. However, Ackerman et al.^[58] did not fit glucose and insulin simultaneously and did not account for homeostasis in their

model. Another difference is that production of insulin depends only on glucose concentrations in this model.

Lima et al.^[103] used a combination of indirect response (IDR) models^[104,105] (see also section 6) to describe stimulation of insulin secretion by glucose and stimulation of glucose utilization by insulin (figure 4). IDR models describe stimulation or inhibition of production or loss of endogenous substances. The four basic IDR models are numbered I to IV and describe inhibition of production, inhibition of loss, stimulation of production and stimulation of loss. The properties of these models have been reviewed.^[106,107] Physiologically, an increase in the blood glucose concentration stimulates insulin secretion by β -cells. The resulting increased insulin concentrations in turn stimulate utilization of glucose by peripheral tissues such as muscle and fat, which leads to a return of glucose concentrations back to baseline (see section 1). Therefore, in a simplified manner, IDR models can adequately describe the physiological situation.

The model by Lima et al.^[103] assumes linear stimulation of the production rate of insulin by a glucose concentration above baseline, as well as linear stimulation of the rate of glucose efflux by insulin above baseline. An additional insulin action compartment, as found in the minimal model, was not needed. In the study, a single dose of terbutaline, which stimulates β_2 -adrenergic receptors and therefore enhances hepatic glucose production by glycogenolysis, was given to healthy subjects. The population pharmacokinetic/pharmacodynamic model adequately described

the increase in glucose concentrations after the terbutaline dose, the subsequent increase in insulin concentrations, and the return to baseline of both glucose and insulin concentrations. By this modelling, it could be established that the β_2 -adrenergic receptor diplotype influences receptor-stimulated glucose production in healthy subjects. Therefore different metabolic effects of drugs influencing the β_2 -adrenergic receptor might be seen in patients with different genotypes. The feedback system in this model can be applied to incorporate and evaluate other drug effects. Because of the feedback between glucose and insulin, estimation of all parameters in such a model can be difficult. Piecewise estimation of the model, fixing the value of some parameters to a physiologically reasonable value for the population, or both, are alternatives if all parameters cannot be estimated simultaneously. In this model, the parameter S_3 (the factor describing the stimulation of glucose utilization by insulin) was fixed to the population mean with a small intersubject variability. The action of insulin was described as stimulation of glucose utilization. Alternatively, it could also be incorporated as inhibition of glucose production by insulin as, in addition to stimulation of glucose utilization, insulin inhibits both gluconeogenesis and glycogenolysis (see section 1). Incorporation of both mechanisms of insulin action is not feasible, as the estimation of all parameters becomes more difficult. Hanze et al.^[108] used a similar approach with IDR models to describe the glucose-insulin system in obese patients treated with metformin. Their model, which was presented in a poster, described stimula-

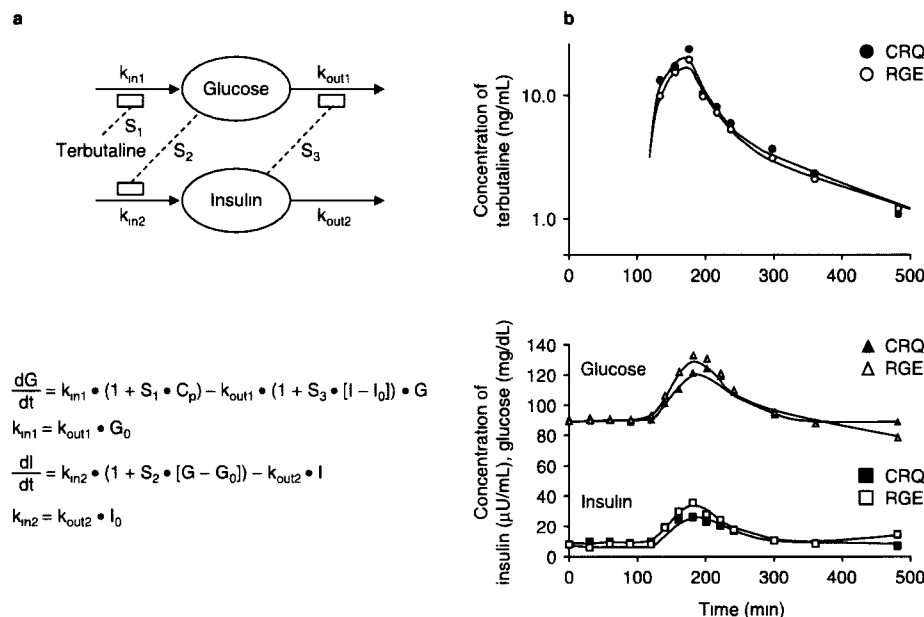


Fig. 4. Model describing feedback between glucose and insulin. CRQ (Cys-19/Arg16/Gln27) and RGE (Arg-19/Gly16/Glu27) are different genotypes of the β_2 -adrenoceptors (adapted from Lima et al.^[103]). S_1 , S_2 and S_3 are stimulation factors. C_p = drug concentration in plasma; G = plasma glucose concentration (mg/dL); G_0 = baseline glucose concentration; I = plasma insulin concentration (μ U/mL); I_0 = baseline insulin concentration; k_{in1} = glucose production rate; k_{in2} = insulin production rate; k_{out1} = disposition rate constant for glucose; k_{out2} = disposition rate constant for insulin; t = time after drug administration.

tion of insulin production by glucose and stimulation of glucose utilization by insulin by sigmoid maximum effect ($E_{\max}$) models.

A similar approach to describing the glucose-insulin system, including feedback in both directions, was applied recently by de Winter et al.^[109] in a population pharmacodynamic model. However, they described insulin action as inhibition of glucose production (figure 5). All of their samples were taken in the fasting state, where the majority of glucose is taken up by insulin-independent tissues such as the brain. Therefore, according to the authors, insulin regulates blood glucose mainly by inhibition of hepatic glucose production. In the fasting state, liver glycogen stores are depleted so that hepatic glucose production is mainly due to gluconeogenesis, which is increased in T2DM patients.^[43]

A more detailed discussion of the model by de Winter et al.^[109] is provided in section 8.

Other models that describe and simulate glucose homeostasis are control-type models that were developed for T1DM and T2DM.^[82,110-114] A goal of some of these models is to be able to build an artificial pancreas. However, most of these models do not seem to have been evaluated against real data.

Tiran et al.^[115] developed a physiologically based model to describe the dynamics of insulin distribution, binding and degradation in numerous tissues in diabetic beagle dogs. The physiological parameters were taken from the literature. Subsequently, the same group combined this insulin model with a previously developed glucose model^[116] to predict glucose disposal in pancreatectomized dogs.^[117] The glucose and insulin concentrations

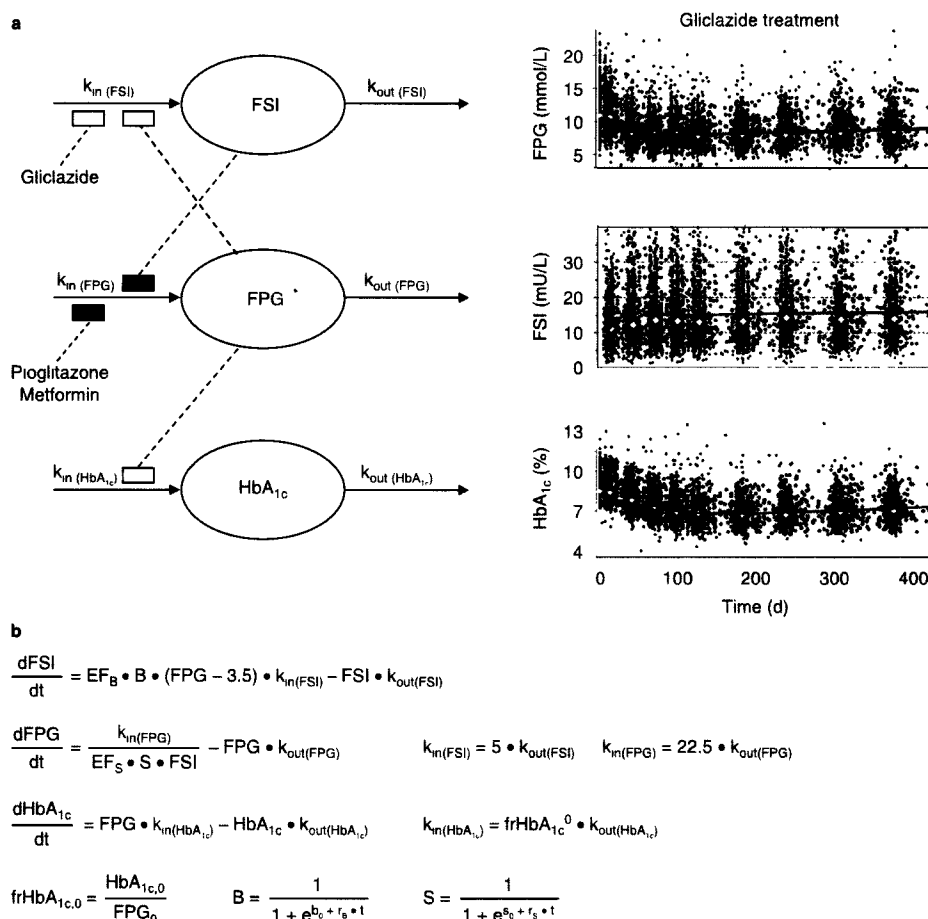


Fig. 5. Model for the long-term effects of glimepiride, metformin, and pioglitazone (adapted from de Winter et al.,^[109] with permission from Springer Science and Business Media). B = fraction of remaining β -cell function relative to healthy persons; b_0 = starting point of disease progression curve for β -cell function; EF_B = factor that describes symptomatic drug effect on β -cell function, if $EF_B > 1$ then β -cell function increases; EF_S = factor that describes symptomatic drug effect on hepatic insulin sensitivity, if $EF_S > 1$ then insulin sensitivity increases; FPG = fasting plasma glucose; FPG_0 = baseline FPG; FSI = fasting serum insulin; $frHbA_{1c,0}$ = estimated $HbA_{1c,0}$ relative to FPG_0 ; HbA_{1c} = glycosylated haemoglobin; $HbA_{1c,0}$ = baseline HbA_{1c} ; k_{in} = zero-order production rate constant; k_{out} = first-order disposition rate constant; r_B = determines the slope of the disease progression curve for β -cell function; r_S = determines the slope of the disease progression curve for insulin sensitivity; S = fraction of remaining hepatic insulin sensitivity relative to healthy persons; s_0 = starting point of disease progression curve for insulin sensitivity; t = time after drug administration.

that were predicted by the model adequately mirrored the observed concentrations.

The clinical utility of a model that describes the glucose-insulin system independently of diagnostic tests is to better understand the regulation of glucose concentrations, which is helpful in developing new drugs. In addition, model parameters can be compared between various groups of patients or subjects to understand the pathophysiology in different groups. Another utility is that drug effects may be incorporated into such a model.

4.3 Models for Important Components of the Glucose-Insulin System

A number of models have been proposed to describe the oscillatory nature of insulin secretion. Insulin secretion is characterized by oscillations on various time scales: oscillations with periods of <1 second, 5–15 minutes (rapid oscillations),^[118] 1–2 hours (ultradian oscillations)^[119] and a circadian rhythm.^[120] A model for simulation of the ultradian oscillations of insulin and glucose concentrations was proposed by Sturis et al.^[121] in the form of a system of six ordinary differential equations. Their model includes stimulation of insulin production by glucose and both inhibition of glucose production and stimulation of glucose utilization by insulin, which is in agreement with the underlying physiology. Two delays, one for stimulation of glucose utilization by insulin and one for inhibition of glucose production by insulin, are included. Their simulated curves result in glucose and insulin concentrations that oscillate around a constant value during the 24-hour period. To evaluate their model, the authors compared their simulated curves with data from subjects receiving a continuous infusion of glucose over 24 hours.^[121,122] The oscillations in the observed data were not as regular and also showed a circadian rhythm that could not be described by the model of Sturis et al.^[121] The authors explained this difference as follows: the simulations are based on parameters that do not change over time, whereas the parameters of complex biochemical processes are unlikely to be constant over time, glucose and insulin may be influenced by factors not accounted for in the model, and rapid pulsations of insulin secretion were observed experimentally. The model was slightly simplified by Tolic et al.^[123] and used as the basis for other modelling efforts by several authors.

Further models for insulin oscillations have been summarized by Makroglou et al.,^[7] who focused on the mathematical properties of the various models. Li et al.^[124] compared several models for ultradian insulin oscillations, developed a delay differential equation model based on the Sturis model^[121] and included a time delay of the glucose-stimulated insulin secretion. Models describing oscillatory insulin secretion can be helpful for understanding of the glucose-insulin system. However, applicability of these models to real data would add further value.

Several authors have developed models for other relevant subsystems. Berman et al.^[125] published a model for distribution, receptor binding and degradation of different types of insulin in rabbits. A model to evaluate insulin receptor kinetics in humans was proposed by Jones et al.^[126] Fuel selection (carbohydrate versus lipid) in muscle tissue in lean and obese individuals was simulated by de Beaudrap et al.^[127] Davis et al.^[128] developed a model for calculation of the threshold for glucose-stimulated insulin release, based on the kinetics of glucokinase. The kinetics of insulin-stimulated translocation of the glucose transporter GLUT-4 in adipose tissue were simulated by Quon.^[39] More recently, Sedaghat et al.^[129] proposed another simulation model to describe insulin signalling pathways that lead to GLUT-4 translocation. The influence of glucokinase activity on insulin secretion was modelled by Sweet et al.^[130] Mosekilde et al.^[131,132] developed a complex model for the absorption of subcutaneous insulin. Osterman-Golkar and Vesper^[133] proposed a simulation model for the glycosylation of haemoglobin, which includes formation of glycosylated haemoglobin (HbA_{1c}) and loss due to expiration of the erythrocyte lifespan, chemical instability and spleen-facilitated erythrocyte clearance. Other models for glycosylation of haemoglobin were developed by Beach^[134] and Shi et al.^[135]

Models that describe specific components of the glucose-insulin system are important for better understanding of the respective subsystem. Moreover, pathophysiological changes that influence the specific subsystem can be elucidated, and the effects of drugs that act on the subsystem may be included.

5. Models for the Glucose-Insulin System Incorporating Drug Effects

When developing models for drug effects, one should first have a model to adequately describe the glucose-insulin system, i.e. to capture the baseline without drug treatment. For long-term studies, disease progression also needs to be considered (see section 8). Therefore, it would be ideal to have a placebo group included in the study. However, because of ethical considerations, this is often not feasible in long-term studies. In addition, the pharmacokinetics of the drug must be adequately described before the drug effect can be added into the model. Usually it is preferable to fit untransformed data. For instance, after an insulin dose, increasing concentrations of insulin and decreasing concentrations of glucose should be fitted instead of an increase in the glucose-lowering effect. In the ideal situation, concentrations of the most relevant biomarkers for the specific mechanism of action should be available. In the majority of studies, only limited measurements (i.e. only plasma glucose concentrations) are available. Therefore, the models have often been simplified and the mechanisms of action have not been incorporated in full detail.

Models that describe the effects of drugs on the glucose-insulin system may be important to characterize the mechanism of action

of a drug. Furthermore, these models may be used to predict the effect of dosage regimens that were not included in the clinical study, or to explore the influence of demographic characteristics or the disease status and disease progression on drug effects.

In this section, published models describing the effects of antidiabetic drugs on glucose, insulin and HbA_{1c} are discussed. Models for drugs that affect other biomarkers that are relevant in diabetes are discussed in section 7. The models in this section are arranged by the type of pharmacodynamic model that they represent. Reviews of the properties and use of mechanism-based pharmacodynamics models are available in the literature.^[136,137] Methods for model evaluation that have been frequently used are visual inspection of predicted versus observed concentrations, standard residual plots, the Akaike information criterion, and the objective function in NONMEM or likelihood-ratio tests in other software. Approaches to model evaluation apart from these standard methods are pointed out for the respective models.

5.1 Biophase Models

In the majority of cases, the drug effect is not immediate but delayed compared with the appearance of the drug in the central circulation. When antidiabetic drugs are given, glucose concentrations often do not decrease immediately, but there is a delay before the effect can be observed. This delay depends on the mechanism of action of the drug. While the time to the onset of the effect is short for exogenous insulin and meglitinides, it can be quite long for agents that influence gene expression, e.g. PPAR γ agonists.

There are various methods to specify a delay between the appearance of drug concentrations in the blood and the onset of the effect. Biophase distribution models were the first approach. Such models assume that the delay is due to the time needed for the drug to diffuse from the blood to the site of action (i.e. the biophase). The term 'biophase' was coined by Furchgott^[138] in 1955. In 1979, Sheiner et al.^[139] proposed a hypothetical effect compartment as a link between plasma drug concentrations and the site of the drug effect. This is mathematically similar to the interpretation by Bergman^[69] of the insulin action compartment in the minimal model.

The drug effect is most often described by a sigmoid E_{max} function (Hill equation^[140,141]), which is driven by drug concentrations in the hypothetical effect compartment. An assumption of the model is that only a negligible amount of the drug is present in the effect compartment, and so the amount of the drug in the effect compartment does not influence the pharmacokinetics of the drug. The time of the maximal effect is delayed relative to maximal plasma concentrations but is dose independent.

Biophase distribution models have been applied by many authors to various antidiabetic drugs with different mechanisms of actions (table IV). Several authors have applied biophase models to describe the effect of exogenous insulin on glucose concentra-

Table IV. Biophase and direct effect models for antidiabetic drugs with various mechanisms of action

Drug effect	Drug	References
Biophase models		
Reduction of glucose concentration	Insulin	142-144
	Glibenclamide (glyburide)	145
	Gliclazide	146
	Tolbutamide ^a	147
	Pramlintide	27
Increase of lactate concentration	Pramlintide	27
Increase in glucose infusion rate during clamp study	Insulin	67
Direct effect models		
Reduction of glucose concentration	Sitagliptin	148
	Troglitazone	149
a Combined with the minimal model and direct effect.		

tions. An early attempt at a pharmacokinetic/pharmacodynamic model for an antidiabetic drug was made in 1987 by Brown et al.^[142] who gave an intravenous bolus of regular insulin to alloxan-induced diabetic dogs and measured serum concentrations of insulin and glucose. Insulin pharmacokinetics were described by two disposition compartments and linear elimination. At the studied dose level, the biophase model could adequately and simultaneously fit the insulin concentrations and the glucose-lowering effect of insulin. The latter was expressed as a fraction of the maximum glucose response.

In 2001, Miyazaki et al.^[143] used the biophase model with a sigmoid E_{max} model to describe the effect of various doses of insulin on glucose concentrations in rats. The authors reported that a biophase model could not fit all doses simultaneously with a single set of parameters. When each dose was fitted separately, the concentration producing 50% of the maximum effect (EC₅₀) values increased linearly with the rate of the insulin infusion. As the EC₅₀ describes the potency of a drug, it should not change with the dose or the rate of administration, except in special cases such as development of tolerance. This suggests that the biophase model could not explain the underlying system sufficiently, and that use of a different approach that takes into account the mechanism of action of insulin would be more appropriate. Indications for development of tolerance in the insulin system were reported in cell culture studies, e.g. desensitization of glucose transport,^[150] insulin receptor downregulation^[151] and slower recycling of the insulin receptors back to the cell membrane after dissociation from insulin.^[152] However, this was reported after continuously high insulin concentrations and not after a single dose.

Biophase models in combination with a Hill function have also been applied to sulfonylureas. In 1997, Rydberg et al.^[145] examined the effect of a single intravenous or oral dose of glibenclamide on blood glucose in healthy subjects by population pharma-

cokinetic/pharmacodynamic analysis. The concentrations of glibenclamide (glyburide) and its two main active metabolites were measured. The combined effect of glibenclamide and the metabolites was described by a competitive model for three agonists. The different EC_{50} values after intravenous and oral doses were explained by the differences in metabolite formation. The authors found lower values of the EC_{50} and the equilibrium rate constant between plasma and the effect compartment (K_{e0}) for the metabolites than for the parent drug, and they concluded that the metabolites have greater potency and a longer duration of effect. This finding might partly explain the lack of a simple relationship between sulfonylurea concentrations and the hypoglycaemic effect, as has been reviewed by Melander et al.^[153] Therefore, including the effects of active metabolites as described might help to elucidate the 'apparently nonexistent' concentration-effect relationship in sulfonylureas.

Another possible complexity might be the development of tolerance due to downregulation of β -cell sensitivity, which takes place under continuously high concentrations of sulfonylureas.^[153] A limitation of the model by Rydberg et al.^[145] is that the mechanism of action of glibenclamide was not directly taken into account. Although sulfonylureas act by stimulation of insulin secretion, insulin concentrations were not available, and a more mechanistic model including the effect of glibenclamide on insulin concentrations could not be developed.

Frey et al.^[146] studied the effect of the sulfonylurea drug gliclazide on FPG in two phase II studies over 8 weeks and two phase III studies over 1 year in T2DM patients. As in the majority of long-term studies, insulin data were not available. Their population pharmacokinetic/pharmacodynamic model included a biophase model with an E_{max} model that was driven by the area under the plasma concentration-time curve (AUC) instead of the concentration. One of the major aims of this model was to identify factors that predict between-subject variability in the response to gliclazide. The main explanatory factor was the number of classes of antidiabetic drugs that the patients had received before entry into the study. This model is discussed further in section 8.

Pramlintide is a synthetic analogue of human amylin (see figure 1 and sections 1 and 2). It is generally administered subcutaneously before meals and is used in T1DM and T2DM patients receiving insulin treatment. In 1996, Colburn et al.^[27] compared the postprandial increase in plasma glucose and lactate after placebo and various doses of pramlintide as an intravenous bolus or infusion in T1DM patients. They used a combination of the biophase model with a sigmoid E_{max} model and found linear pharmacokinetics and concentration-dependent effects on glucose and lactate within their studied dose range. However, curve fits were not provided. As described for other studies above, the values of the K_{e0} and EC_{50} increased with the dose. These data would be more appropriately characterized with an IDR model.

5.2 The Minimal Model

The minimal model was originally developed for evaluation of the IVGTT (see section 4.1^[54]). More recently, the minimal model or extensions of this model have been employed to study drug effects. An overview of the applications is given in table V. Some authors performed studies that included a diagnostic test such as a euglycaemic clamp, IVGTT or meal test, which was performed with and without the drug under investigation. The results of both treatments were modelled, and the parameters were compared between the treatments with and without the drug.^[154-157]

Agerso and Vicini^[154] adapted the minimal model to simultaneously fit glucose and insulin concentrations during an IVGTT after single doses of liraglutide in healthy subjects. First-phase insulin secretion was included in the model by an empirical Gaussian function. In this model, the drug effect was not included, but the parameter estimates were compared between placebo and various doses of liraglutide. The individual parameter estimates were plotted against the drug concentration at the time of the start of the IVGTT to identify possible relationships. For modelling, the standard two-stage approach was used and subsequently the first-order method in NONMEM.

Mager et al.^[66] adapted the model from Agerso and Vicini^[154] to include the effect of exenatide (exendin-4), another incretin mimetic, on insulin secretion. The drug effect is included as a Hill function that is added to the parameter γ in the equation for plasma insulin (see figure 3). This model was applied to data from a hyperglycaemic clamp study in healthy subjects and diabetic patients. By use of this model, the concentrations of glucose and insulin after infusion of exenatide during the clamp study could be well described. The authors concluded that the T2DM patients had a decreased capacity to enhance insulin release compared with healthy subjects.

Rostami-Hodjegan et al.^[158] modelled the effects of tolbutamide on glucose and insulin concentrations during euglycaemic and hypoglycaemic clamp studies. In their population model, insulin secretion is affected by tolbutamide concentrations, both in the central compartment and in a 'remote effect compartment', whereas glucose concentrations are fitted by empirical functions. In a separate part of the model, the effects of insulin and tolbutamide on glucose concentrations were modelled with insulin concentrations described by an empiric function. Model parameters including the insulin sensitivity index, glucose effectiveness and the elimination rate constant of insulin from the remote effect compartment (lymph), which is different from the rate constant for transfer of insulin to the lymph, were estimated in the presence and absence of tolbutamide. The authors concluded that in addition to stimulation of insulin secretion, tolbutamide prolongs the residence time of insulin in a remote effect compartment and therefore prolongs the effect of insulin. Kirchheiner et al.^[147,159] reported

Table V. Minimal model for drugs that stimulate insulin production

Drug	Comments	Reference
Liraglutide	IVGTT Comparison of parameters at different doses Glucose and insulin modelled simultaneously Both feedbacks included	154
Exenatide (exendin-4)	Hyperglycaemic clamp Glucose and insulin modelled simultaneously Both feedbacks included	66
Insulin (regular and aspart)	Euglycaemic clamp Comparison of parameters for regular insulin and insulin aspart Glucose and insulin modelled simultaneously No feedback of glucose on insulin	155
Tolbutamide	Hypoglycaemic and euglycaemic clamp Effect of insulin and tolbutamide on glucose, and effect of tolbutamide and glucose on insulin modelled separately	158
Tolbutamide	Single dose followed by three doses of oral glucose	147
Glibenclamide (glyburide)	Single dose followed by three doses of oral glucose	159
Adrenaline	Two-compartment minimal model for labelled IVGTT Comparison of parameters with and without adrenaline	156
Glimepiride	Combined with IDR model III Glucose and insulin modelled simultaneously No feedback of glucose on insulin	160
Vildagliptin	Comparison of parameters with and without vildagliptin Minimal model for meal tests	157

IDR = indirect response; IVGTT = intravenous glucose tolerance test.

that they adapted the model from Rostami-Hodjegan et al.^[158] to describe the effects of tolbutamide^[147] and glibenclamide^[159] on insulin secretion in healthy subjects. However, the equations were not reported. The pharmacodynamic parameter estimates were not reported, except for the $E_{\max}$ and EC_{50} for the tolbutamide study.

Yun et al.^[160] developed a model that combines a variant of the glucose disappearance model (figure 3) from the minimal model with an IDR model to describe the effect of glimepiride on insulin secretion and glucose disappearance. Single doses of glimepiride or placebo were given to six healthy subjects. Glimepiride, insulin and glucose concentrations were measured. Glimepiride concentrations in plasma were modelled by a two-compartment disposition model with both mixed-order (Michaelis-Menten) absorption and elimination using the standard-two-stage approach. IDR model III was used to describe the stimulation of insulin secretion by glimepiride. The glucose-insulin system was described similarly to the glucose disappearance part of the minimal model, with the difference being that glucose is affected directly by insulin from the central compartment, and no insulin effect compartment is included in the model by Yun et al.^[160]

This model takes into account the mechanism of action of sulfonylurea drugs, and insulin and glucose are modelled simultaneously. However, the model was not fitted to glucose and insulin concentrations directly, which is preferable, but the increases in

insulin secretion and glucose disappearance compared with placebo were fitted. By this approach of correcting for the baseline concentrations (placebo treatment), the increase in glucose concentrations due to a meal that was given 4 hours after the dose was included in the model. If possible, it is preferable to model the data directly, both after placebo and after drug treatment, instead of modelling the change from baseline as in the model by Yun et al.^[160]

5.3 Indirect Response Models

Many authors have employed IDR models to describe antidiabetic drug effects (table VI). These models can be used to describe the underlying physiology of the glucose-insulin system.

An early application of an IDR model to antidiabetic drug effects was reported by Benincosa and Jusko in 1999.^[163] The compartmental structure and equations in the model are shown in figure 6. A 26-week clinical trial with various dosing regimens of oral rosiglitazone was performed in patients with severe T2DM. FPG and HbA_{1c} were measured, and rosiglitazone pharmacokinetics were predicted from another trial. The model describes the effect of rosiglitazone on FPG as stimulation of glucose utilization (figure 6). This mirrors one of the main mechanisms of action of thiazolidinedione antidiabetics (see section 2).^[11] The delay in the onset of rosiglitazone action due to gene transcription was includ-

ed in the model by use of a transduction compartment. The stimulation of glucose utilization is described by a sigmoid $E_{\max}$ function driven by rosiglitazone concentrations.

The FPG profile over time could be successfully modelled simultaneously for placebo and four different dosage regimens of rosiglitazone. The maximum decrease in FPG was estimated at 160 mg/L, and the drug concentration at half-maximal effect (stimulation) $[SC_{50}]$ for rosiglitazone was about 50 ng/mL. Simulations from the model showed that for the maximum glucose-lowering effect, the rosiglitazone concentrations should remain above a threshold of twice the SC_{50} for most of the dosing interval. Therefore, an increased effect of a sustained-release product could be predicted by use of modelling. This model is an example of how the choice of optimized dosage regimens can be supported by pharmacokinetic/pharmacodynamic modelling and simulation of antidiabetic drug effects.

To our knowledge, this model was the first one that included concentrations of HbA_{1c} . The production of HbA_{1c} is described as a first-order process, which is proportional to the FPG concentrations. The glycosylation of haemoglobin is theoretically a second-order reaction between haemoglobin and glucose. However, as the total haemoglobin concentration in blood is large compared with the fraction that is glycosylated, it is not changed sufficiently by the reaction with glucose (a pseudo first-order reaction). The elimination of HbA_{1c} is modelled as a first-order process with a degradation rate constant. Although the elimination of HbA_{1c} depends on the lifespan of the erythrocytes, it can be described as a first-order process when the concentration of haemoglobin is assumed to be at steady state. With this model, the HbA_{1c} concentrations after placebo and various doses of rosiglitazone could be captured well over the 26 weeks of the treatment.

Recently, Hamrén et al.^[164,166] used a model similar to the rosiglitazone model described above in a population pharmacokinetic/pharmacodynamic analysis of the effect of various doses of tesaglitazar or placebo on FPG during 12 weeks of treatment in T2DM patients. The development of tesaglitazar, a $PPAR\alpha/\gamma$ agonist for treatment of glucose and lipid abnormalities, was

discontinued in phase III of clinical development. The concentrations of tesaglitazar, FPG, HbA_{1c} and haemoglobin were measured and could be adequately described by the model (figure 7). A common undesired effect of $PPAR$ agonists is oedema. In the study, a decrease in the haemoglobin concentrations was observed in the group treated with tesaglitazar. Thus haemoglobin concentrations were not at steady state. In comparison with the model by Benincosa and Jusko,^[163] the authors used an expanded model for glycosylation of haemoglobin, which mirrors the erythrocyte lifespan and employs several transit compartments to describe the different ages of the erythrocytes. The glycosylation of haemoglobin is described by a power function and is proportional to the glucose concentration. The proportion of HbA_{1c} increases with the age of the erythrocytes. For model qualification, the estimated relationship between FPG and HbA_{1c} was compared with data from four publications in the literature. The model by Hamrén et al.^[164,166] is an advanced HbA_{1c} model that can be used when haemoglobin concentrations are changing.

Lin and Chien^[144] applied the IDR approach in 2002 to describe the effect of an intravenous bolus dose of regular human insulin on plasma glucose in minipigs. The standard two-stage approach was used for model fitting. The authors tested a biophase model and concluded that it was not possible to successfully describe their data by use of a biophase model only. Both IDR models I and IV could adequately fit the observed glucose concentrations, although addition of an effect compartment might have improved the curve fits. On the basis of the statistical criteria, IDR model IV was preferred over IDR model I. Besides statistical criteria for model selection, the mechanism of action of the drug should be appropriately incorporated. For the mechanism of action of insulin, both inhibition of production and stimulation of utilization of glucose are relevant. As insufficient data are usually available to include both of these mechanisms in the model, one needs to decide which mechanism might be more important for the particular situation. Moreover, often an IDR model for stimulation of utilization and an IDR model for inhibition of production can describe a set of data

Table VI. Indirect response (IDR) models for antidiabetic drugs with various mechanisms of action

Mechanism of drug action	Drug	IDR model nos.	References
Inhibition of glucose production	Insulin	I	144
	Metformin	I	109,161
	Pioglitazone	I	109
Stimulation of insulin production	Gliclazide	III	109
	Glimepiride	III ^a	160
Stimulation of glucose utilization	Insulin	IV	144,162
	Rosiglitazone	IV	163
	Tesaglitazar	IV	164
Inhibition of glucose production and stimulation of glucose utilization	Metformin	I + IV	165

a IDR model III in combination with minimal model.

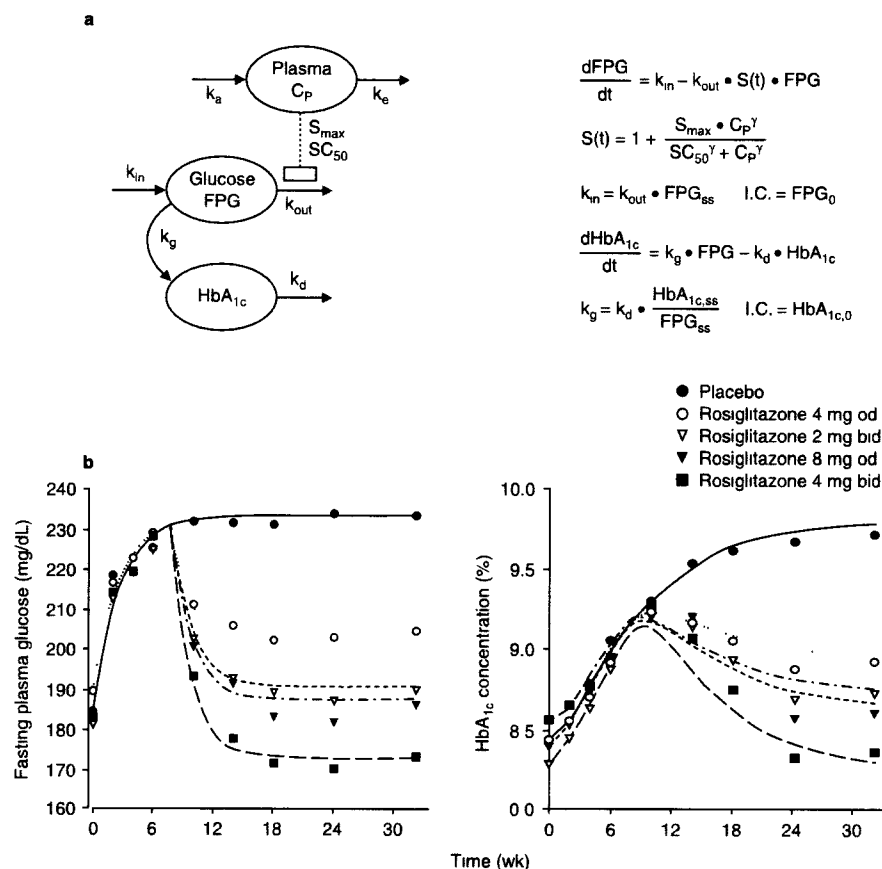


Fig. 6. Model describing the effect of rosiglitazone on glucose and glycosylated haemoglobin (HbA_{1c}).^[163] γ = Hill coefficient; **bid** = twice daily; **C_P** = drug concentration in plasma; **FPG** = fasting plasma glucose; **FPG₀** = FPG at time $t = 0$; **FPG_{ss}** = FPG at steady state; **HbA_{1c}** = glycosylated haemoglobin; **HbA_{1c,0}** = HbA_{1c} at time $t = 0$; **HbA_{1c,ss}** = HbA_{1c} at steady state; **I.C.** = initial condition; **k_a** = first-order absorption rate constant; **k_d** = first-order rate constant for degradation of HbA_{1c}; **k_e** = elimination rate constant; **k_g** = rate constant for glycosylation of haemoglobin; **k_{in}** = zero-order production rate constant; **k_{out}** = first-order disposition rate constant; **od** = once daily; **SC₅₀** = drug concentration at half-maximal effect (stimulation); **S_{max}** = maximum effect; **S(t)** = stimulation function.

equally well and, with only curve fitting, it cannot be decided which one is the more relevant mechanism of action.

Gopalakrishnan et al.^[162] used IDR model IV for a dose of intravenous or inhaled (spray instillation) insulin in rats. The population pharmacokinetic/pharmacodynamic model describes the insulin effect as stimulation of glucose utilization. The value of the SC_{50} was fixed to an estimate from the literature. However, they had a more complex model for the pharmacokinetics of insulin administered by spray instillation, including both first- and zero-order absorption.

In 2004, Lee and Kwon^[161] used IDR model I to model the effect of a single oral dose of metformin in healthy subjects using the standard two-stage approach. With this basic model, which describes the metformin effect as inhibition of glucose production, they could fit the observed glucose concentrations from their study reasonably well. Inhibition of glucose production was often reported as one of the mechanisms of action of metformin; therefore, the model of Lee and Kwon^[161] mirrors part of the mechanism of

action of metformin. A limitation of the modelling is that the glucose concentrations were not modelled directly, but the plasma glucose-lowering effect of metformin as a percentage change from baseline was modelled. Most recently, Hong et al.^[167] applied an approach similar to the model by Lee and Kwon.^[161] Data on FPG from T2DM patients receiving multiple doses of metformin were described by IDR model I. A linear model was used to relate the slightly increasing plasma lactate concentrations to metformin concentrations.

A more elaborate model for the action of metformin was developed by Stepensky et al.^[165] in 2002 (data shown in figure 7). Metformin was given to streptozocin-induced diabetic rats as a bolus or infusion by the intravenous, intraduodenal and intraportal routes. The rates of infusion were adjusted in a way that the metformin plasma concentration-time profiles were similar for all three routes of administration. Despite the similar metformin plasma concentrations, the glucose-lowering effect was larger after intraduodenal infusion than after intraportal infusion, and

smallest after intravenous infusion. The authors developed a model that includes a combination of IDR models and describes the effect of metformin at three different sites of action: (i) stimulation of glucose utilization in the gut; (ii) inhibition of hepatic glucose production; (iii) and stimulation of glucose utilization in muscle and fat. In contrast with most other models, the drug flux through the intestinal microvessels and the portal vein was used as a driving force for the effects in the gut and liver, and not the concentration of metformin at those sites of action. The authors reported that a model with drug concentrations as a driving force for the effects in the gut and liver could not describe the time course of the effect. With this model, various mechanisms and sites of action of metformin could be described.

From their modelling, the authors concluded that, in addition to the most often cited effect of metformin on glucose production, the effect in the gut is important.^[165] If the drug is given intraportally or intravenously, it does not reach the site of action in the gut, and the effect on glucose concentration is smaller. The authors called

this a “first-pass pharmacodynamic effect”.^[165] An increase of anaerobic glucose metabolism in the gut by metformin has been reported previously.^[11] Therefore, such a complex model can be used to investigate the mechanism of drug action, as this model was based on administration of metformin via different routes. More complex studies are often needed to support models that are detailed enough to draw conclusions about the mechanism of action. This model also shows an example where a combination of IDR models was used and, with the addition of a relatively small number of parameters, various mechanisms of action could be included.

Hanze et al.^[108] presented a model for the effect of metformin on the glucose-insulin-HbA_{1c} system in obese patients with T2DM. They concluded that after 6 weeks of treatment, the main pharmacodynamic effect of metformin seemed to be a reduction in gluconeogenesis by about 37%, and HbA_{1c} was reduced by about 0.3% with metformin.

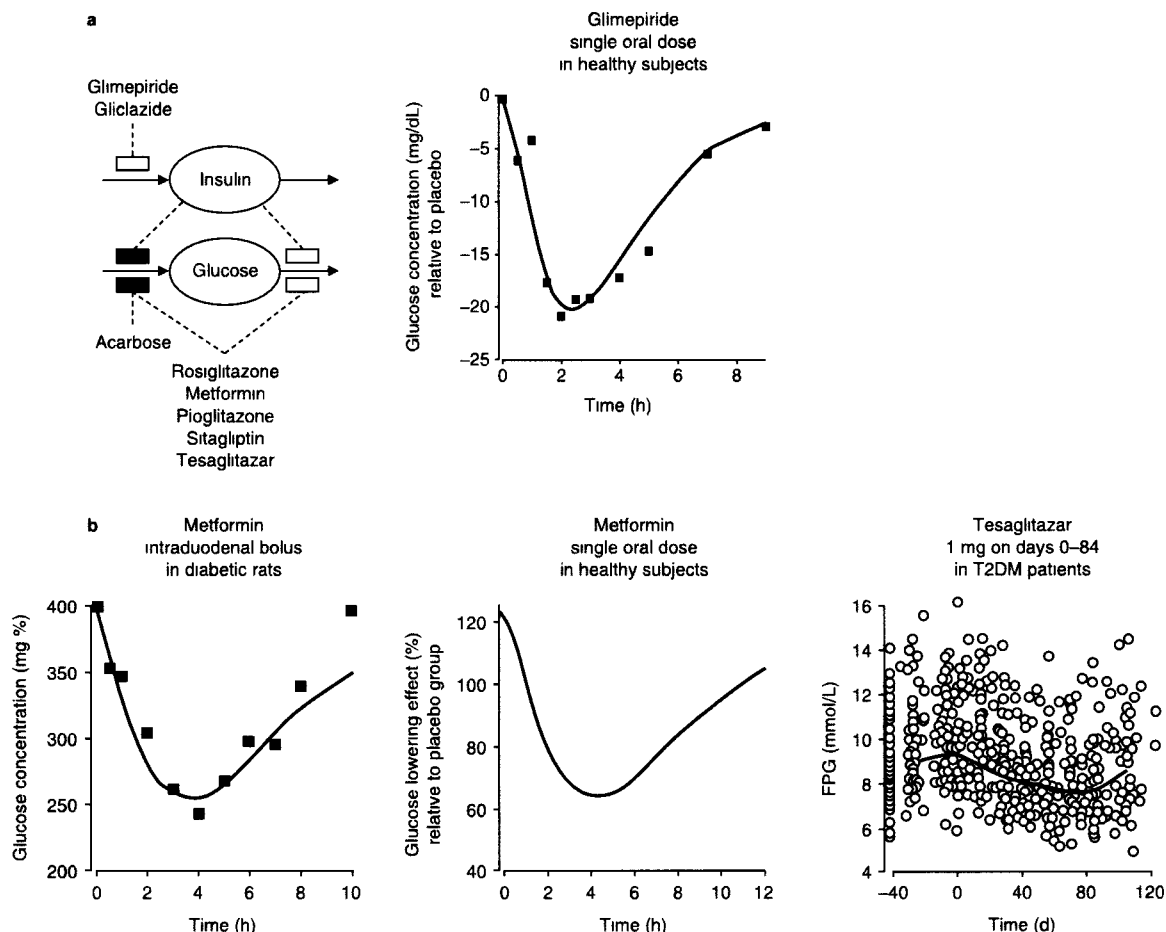


Fig. 7. Indirect response models describe various mechanisms of action that result in a decrease in glucose concentrations (adapted from Yun et al.,^[160] Stepensky et al.,^[165] and Hamrén et al.,^[164] with permission; simulation from Lee and Kwon^[161]). **FPG** = fasting plasma glucose; **T2DM** = type 2 diabetes mellitus.

A population pharmacodynamic model that is based on a combination of IDR models was developed by de Winter et al.^[109] (figure 5), using two studies with a total of 2408 T2DM patients who received treatment with metformin, gliclazide or pioglitazone over 1 year. Fasting serum insulin, FPG and HbA_{1c} were measured, but pharmacokinetic data for the three antidiabetic drugs were not available. The authors described the effect of metformin on FPG by IDR model I for inhibition of glucose production. However, they reported a model misspecification and pointed out that their results for metformin should be interpreted with caution. In agreement with Stepensky et al.,^[165] the authors concluded that this result could suggest that inhibition of glucose production might not be the main mechanism of action of metformin. Furthermore, the model of de Winter et al.^[109] described the effect of gliclazide on insulin by IDR model III for stimulation of insulin production, which could adequately fit the data. The effect of pioglitazone on FPG was modelled by IDR model I for inhibition of glucose production although, in general, the major mechanism of action of thiazolidinediones is stimulation of glucose utilization. As for the action of insulin (see section 4.2), the authors justified this choice by stating that in the fasting state, most of the glucose is taken up by insulin-insensitive tissues. Therefore, inhibition of glucose production was chosen as the more relevant mechanism of action of pioglitazone in this situation.^[109] For glycosylation of haemoglobin, the model developed by Benincosa and Jusko^[163] was applied. The disease progression model applied by de Winter et al.^[109] is described in section 8.

Antidiabetic drugs have various mechanisms to lower glucose concentrations. IDR models can be utilized to describe these different mechanisms of action and the data from various drugs. This is shown for a decrease in glucose concentrations in figure 7.

We compared the estimates for the first-order disposition rate constant for endogenous compounds (k_{out}) parameter, which describes first-order loss of glucose from plasma (e.g. due to tissue utilization) among the available publications in which IDR models were used to describe the glucose-insulin system. Average estimates for the k_{out} were about 1.1–1.6 h⁻¹ in pigs,^[144] 0.33 h⁻¹ and 0.42 h⁻¹ in rats,^[162,165] and 0.68 h⁻¹ to 4.3 h⁻¹ in healthy subjects.^[103,161,168] This corresponds to a half-life of glucose in plasma of 10 minutes to 1 hour in healthy subjects. In the minimal model, loss of glucose from plasma at basal insulin concentrations is described by the glucose effectiveness parameter, S_G . Among the authors who used the minimal model to describe drug effects in healthy subjects, Agero and Vicini^[154] and Osterberg et al.^[155] reported S_G estimates corresponding to a glucose half-life of 0.5 hours, whereas Rostami-Hodjegan et al.^[158] found S_G values corresponding to half-lives of between 9 minutes and 1.3 hours from five different studies. This range is similar to the range of half-lives found in studies employing IDR models. From one study in which an IDR model and the minimal model were combined, a

very small elimination rate constant of 0.012 h⁻¹ was reported for glucose.^[160]

Estimates of the k_{out} of insulin in healthy subjects were about 6.1–8.0 h⁻¹^[103] and 0.89 h⁻¹^[160] from two studies, i.e. the half-lives of insulin in plasma would be about 5 minutes, which is frequently reported, or 47 minutes. The k_{out} for FPG in long-term studies in a large number of T2DM patients was more similar between the three reported models: 0.021 day⁻¹,^[109] 0.037 day⁻¹^[164] and 0.055 day⁻¹.^[163] Based on these estimates, it would take between 50 and 130 days (2–3 months) to reach a new steady state for FPG, e.g. after a change in antidiabetic treatment. Average estimates for the k_{out} of HbA_{1c} were 0.019 day⁻¹^[163] and 0.027 day⁻¹.^[109] This corresponds to a time to the new steady state of 102–144 days and is in agreement with the erythrocyte lifespan of about 120 days. Hamrén et al.^[164] estimated an erythrocyte lifespan of 136 days from their transduction model. Similar estimates of 0.44^[163] and 0.66^[164] for the maximum stimulation effect (S_{max}) of the PPAR agonists rosiglitazone and tesaglitazar on glucose utilization were reported. Based on these estimates, if the drugs reach sufficiently high concentrations, the rate of glucose elimination from plasma can be increased by 44% or 66%. Estimates of the S_{max} for stimulation of glucose utilization by insulin were about 5.8 from a study in rats^[162] and about 4.9 from a study in pigs.^[144]

Models such as the basic IDR models I or IV have been used successfully to fit glucose concentrations after a single dose of insulin or metformin.^[144,161] If observed concentrations for pharmacokinetics and pharmacodynamics after administration of the drug via different routes of administration or different doses are available, or if more than one biomarker has been measured, more complex models that better mirror the mechanisms of action can be built.

5.4 Use of Biophase Models versus Indirect Response Models

Biophase models are most appropriate when the delay in drug action truly originates from distribution to the site of action. However, this modelling approach is often applied inappropriately when the most relevant underlying process that causes the delay is not drug distribution. For the action of antidiabetic drugs, other reasons (e.g. turnover of biomarkers such as glucose, signalling pathways [transduction] or translocation of glucose transporters) might be more relevant. Whereas data from one dose level can be adequately fitted by biophase models, data from different doses usually cannot be fitted simultaneously with one set of parameters. In addition, the turnover and homeostasis of glucose and insulin is not accounted for by biophase models.

The basic IDR models describe a drug mechanism that immediately alters the production or loss of endogenous substances, and therefore are most useful when the turnover (e.g. glucose concentrations) can be measured directly. Sometimes other processes

precede this effect, and then IDR models can be combined with biophase distribution or signal transduction models. Several studies have inappropriately applied a biophase model when the starting model should have been an IDR.^[27,142,143,145,146] However, some of these studies were published before IDR models became widely appreciated.

In euglycaemic hyperinsulinaemic clamp studies, the feedback between glucose and insulin is disrupted, and the endogenous insulin production is assumed to be zero. The effect of an exogenous insulin dose is described by the GIR, which is assumed to be equal to the glucose utilization rate. Therefore, either a direct effect model or a biophase distribution model can describe the GIR during a euglycaemic hyperinsulinaemic clamp study, when there is a delay between insulin profiles and the GIR (for example, see figure 8). The biophase model^[64,67] and the remote insulin compartment in the minimal model (figure 3) function similarly to account for a delay in insulin action.

6. Models that Describe Secondary Drug Effects

Models that describe drug effects on the glucose-insulin system are not only applicable to antidiabetic drugs; there are numerous other agents that can influence glucose concentrations. Examples are adrenoreceptor agonists^[103,168,169] or antagonists,^[170] monoamine oxidase inhibitors, immunosuppressants (corticosteroids, tacrolimus, sirolimus^[171]), antipsychotics (chlorpromazine,^[172] clozapine, olanzapine^[173-176]), gatifloxacin,^[177-179] thiazide diuretics,^[180] diazoxide,^[181] acipimox^[182] and hormones such as somatostatin.^[181] The secondary effects on glucose concentrations can pose

an important limitation to the use of some of these drugs in diabetic patients. Therefore, models that describe these secondary effects can be helpful to predict adverse events in diabetic patients. Although numerous models are available for the effects of antidiabetic drugs, only a few authors have developed models to describe secondary drug effects on glucose and insulin that can cause adverse effects for the patients. An overview of models that have been proposed is shown in table VII.

In 1988, Sato et al.^[184,185] developed a model to describe hyperglycaemia after administration of three different doses of chlorpromazine to rats. Increased concentrations of adrenaline, noradrenaline, glucose and insulin were observed after the chlorpromazine dose. The glucose-insulin system was described by a set of two differential equations that are similar to the pioneer model by Bolie.^[50] As in the Bolie model, insulin secretion depends only on glucose concentrations, and the homeostasis of glucose and insulin is not taken into account. It was assumed that the relevant biophase for the effect is the chlorpromazine concentration in the brain. In the model, the calculated chlorpromazine brain concentrations stimulate production of adrenaline and noradrenaline which, in turn, stimulate production of glucose and inhibit production of insulin. The concentrations of adrenaline, noradrenaline, glucose and insulin could be adequately described by this early mechanism-based model.

It is well known that corticosteroids (also called glucocorticoids) exhibit a variety of metabolic effects. High doses can increase gluconeogenesis and decrease glucose uptake and utilization, both resulting in increased plasma glucose concentrations.

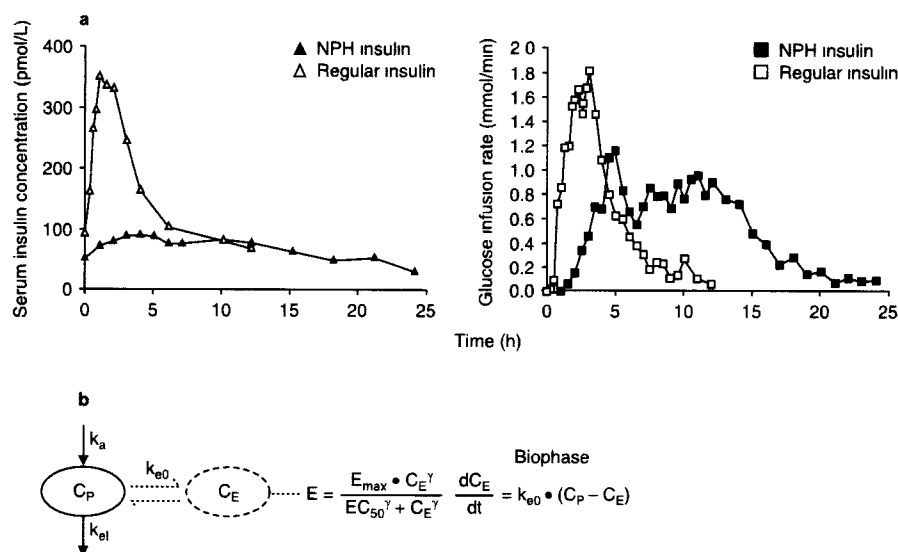


Fig. 8. Biophase model for a euglycaemic clamp study with single doses of subcutaneous insulin (adapted from Woodworth et al.,^[67] with permission from the American Diabetes Association). γ = shape factor that describes the slope of the sigmoidal concentration-effect curve; C_E = drug concentration in the effect compartment; C_P = drug concentration in plasma; E = measured or observed effect; EC_{50} = concentration of the drug producing 50% of the maximum effect; E_{max} = maximum effect; k_a = absorption rate constant; k_{e0} = equilibrium rate constant between plasma and the effect compartment; k_{el} = elimination rate constant; **NPH insulin** = neutral protamine Hagedorn insulin with an intermediate duration of action; t = time after drug administration.

Table VII. Models describing secondary drug effects

Mechanism of drug action	Drug	Model	References
Stimulation of glucose production	Salbutamol (albuterol)	Linear direct effect	169
	Salbutamol	IDR III	168
	Terbutaline	IDR III	103
	Glucocorticoids	E _{max} model ^a	183
	Catecholamines	Model on feedback	184
Stimulation of catecholamine production	Chlorpromazine	Model on feedback	184,185
Inhibition of insulin production	Catecholamines	Model on feedback	184

a Effect driven by pharmacokinetics in the second compartment.

E_{max} = maximum effect; IDR = indirect response.

Derendorf et al.^[183] developed a model to describe the changes in glucose concentrations after intravenous single doses of dexamethasone, methylprednisolone, triamcinolone acetonide or placebo in healthy subjects. They used a two-compartment model for the corticosteroid pharmacokinetics and calculated the non-protein-bound concentrations in the peripheral compartment. These free concentrations were then entered into an E_{max} model including a lag time to predict the glucose concentrations. Pharmacodynamic parameters from previous studies of corticosteroids were used to predict the glucose concentrations from the current study. The simulated glucose concentration-time curves could mirror the areas under the observed concentrations reasonably well, although the shapes were different. In the usual biophase model, effect-compartment concentrations that can be adjusted during the modelling without any influence on the plasma pharmacokinetics are estimated. A more complex and mechanism-based model for the metabolic effects of corticosteroids is discussed in section 7.

Another group of drugs that can induce hyperglycaemia are β_2 -adrenoreceptor agonists, which are used for bronchodilation in asthma patients. Stimulation of hepatic β -adrenoreceptors induces glycogenolysis and hence release of glucose from the liver.^[186] In 1998, Gumbhir-Shah et al.^[169] characterized the increasing glucose concentrations after an inhaled dose of albuterol in healthy subjects, using a linear effect model. The same group performed a study in asthmatic subjects who received salbutamol (albuterol) by nebulization.^[168] The increase in glucose concentrations after the dose could be described by IDR model III with a linear stimulation of glucose production by salbutamol. In 2004, Lima et al.^[103] developed an improved model to describe the effects of a single intravenous infusion of terbutaline in healthy subjects (figure 4). As for salbutamol, the effect of terbutaline was modelled by IDR model III for stimulation of glucose production. In contrast to the two previous models, not only terbutaline and glucose but also insulin concentrations were available and were included in the model. As described in section 4.2, the intrinsic reciprocal feedback relationship between glucose and insulin was described by a combination of two IDRs. The increase and return to baseline of

glucose and insulin concentrations after a terbutaline dose could be adequately fitted by this model. Thus the model for terbutaline effects is an advanced model based on the previous models for salbutamol, and the most important improvement is the addition of the feedback between glucose and insulin. This feedback model could be used as the basis for modelling the effects of other drugs.

7. Models that Describe Effects on Ancillary Biomarkers

In addition to the most established biomarkers, which are glucose, insulin and HbA_{1c}, a long list of other endogenous substances is under investigation as potential biomarkers for diabetes. The role of biomarkers in drug development and pharmacokinetic/pharmacodynamic modelling, including definitions and classifications for biomarkers, has been reviewed.^[187-189] Examples of possible ancillary biomarkers in diabetes are FFA, triglycerides, glucagon, sorbitol, C-peptide, PEPCK, 11 β -hydroxysteroid dehydrogenase 1, fructosamine, GLP-1, GIP, adiponectin, leptin and cytokines such as TNF- α or interleukin-6. Models that describe drug effects on ancillary biomarkers may be important to evaluate which biomarkers (i) are most useful for studying drug effects, (ii) mirror disease progression in diabetes, and (iii) should be measured in future studies and clinical practice. In addition, the effects of other dosage regimens of the drug on a biomarker can be predicted. Table VIII gives an overview of models that have been proposed to describe concentrations of ancillary biomarkers.

Recently, an increasing body of data has supported the role of inflammation and inflammatory cytokines such as TNF α in the development of insulin resistance and T2DM.^[196] Models for the distribution and effects of TNF α have been proposed, but not in the context of diabetes.^[197,198]

The role of FFA in the regulation of glucose metabolism has become increasingly appreciated^[199] (see also section 1). The effect of an adenosine A₁ receptor agonist, which has been in development as an antilipolytic agent, on FFA in diabetic rats was modelled by van Schaick et al.^[192] The drug or placebo was administered as a single dose to lean and obese Zucker rats. The change in FFA concentrations with treatment relative to FFA

concentrations after placebo was modelled by IDR model I for inhibition of production of FFA. This basic model could adequately describe the FFA concentration-time profiles for lean and obese rats. The modelling suggested a decreased potency of the drug in obese rats. The authors used an empirical solution for the IDR model to fit their data instead of exact differential equations, which are preferable.^[200] Subsequently, the same group applied a variant of the described model to the effects of six different adenosine A₁ receptor agonists in rats.^[193] In this case, the Hill function for description of the drug effect was replaced by the operational model of agonism (Black and Leff^[201]).

A more complex model for FFA concentrations that includes glucose and insulin was proposed by Roy and Parker^[81] in 2006. They adapted the original minimal model by approximately doubling it, i.e. they added a second insulin effect compartment that acts on the production and loss of FFA. The model includes stimulation of FFA utilization by insulin, and inhibition of FFA utilization and stimulation of FFA production by glucose. FFA concentrations in an effect compartment stimulate glucose production and inhibit glucose utilization. As in the original minimal model, there is no effect of glucose on insulin. This complex model was estimated in pieces and applied to FFA concentrations measured in healthy subjects during a euglycaemic clamp study^[202] and in other published data. However, curve fits to glucose, insulin and FFA concentrations from the same study were not shown. The authors suggest that their model could be helpful to improve predictions of plasma glucose concentrations after mixed meal tests (i.e. meals containing carbohydrates and fat), but further evaluation of the model would be needed.

Another lipid marker that is relevant in diabetes is the plasma triglyceride concentration. PPAR α is an important regulator of hepatic lipid metabolism, and PPAR α agonists such as fibric acid derivatives can decrease triglyceride concentrations in the blood.

The effect of tesaglitazar, a PPAR α/γ agonist (see also section 2), on fasting triglyceride concentrations during a 12-week study in 240 nondiabetic, insulin-resistant subjects was described by Hamrén et al.^[191] IDR model I for inhibition of the production of triglycerides was used to model the response to tesaglitazar. Simulated curves for triglyceride concentrations at different doses were shown, but no model fits to the observed data were provided.

Like tesaglitazar, tolrestat was a drug in development for treatment of diabetic patients, but was discontinued. Tolrestat is an inhibitor of aldose reductase, an enzyme that converts glucose to sorbitol. As high intracellular concentrations of sorbitol are thought to lead to biochemical alterations that result in nephropathy, retinopathy and neuropathy, tolrestat sought to decrease the long-term complications of hyperglycaemia in diabetic patients. van Griensven et al.^[190] studied the effect of single and multiple doses of tolrestat on sorbitol concentrations in erythrocytes from healthy subjects and T1DM patients. IDR model I was used to describe the inhibition of production of sorbitol by tolrestat. Concentrations of tolrestat and sorbitol in healthy subjects and patients could be adequately described by the model, utilizing a standard two-stage approach. The results of the modelling suggested that diabetic patients had a lower zero-order production rate (k_{in}) and k_{out} , but a higher baseline level of sorbitol than healthy subjects. The estimates for the 50% inhibitory concentration were similar in both groups and also similar to results from *in vitro* studies. Although several aldose reductase inhibitors have been withdrawn from clinical trials, some are still under investigation, and epalrestat is marketed in Japan.^[203]

As discussed in section 6, treatment with corticosteroids can enhance hepatic glucose production and therefore result in higher glucose concentrations. Corticosteroids increase gluconeogenesis by induction of gluconeogenic enzymes such as PEPCK, which is the rate-limiting step of gluconeogenesis. A pharmacokinetic/

Table VIII. Models describing ancillary biomarkers

Mechanism of drug action	Drug	Model	Reference
Inhibition of sorbitol production	Tolrestat	IDR I	190
Inhibition of triglyceride production	Tesaglitazar	IDR I	191
	Troglitazone	Direct dose-effect model	149
Effect of FFA on glucose	NA	Extended minimal model	81
Inhibition of FFA production	Adenosine A ₁ receptor agonist	IDR I with E_{max} model	192
		IDR I with operational model of agonism	193
Glycosylation of haemoglobin	Rosiglitazone	IDR I	163
	Tesaglitazar	Transduction model	164
Effect of corticosteroids on PEPCK regulation	Methylprednisolone	PK/PD/PG model including multiple mechanisms	194
C-peptide kinetics	NA	Various extended minimal models	9
Glucagon	NA	Model for control of glucose homeostasis	195

E_{max} = maximum effect; FFA = free fatty acids; IDR = indirect response; NA = not applicable; PD = pharmacodynamic; PEPCK = phosphoenolpyruvate carboxykinase; PG = pharmacogenomic; PK = pharmacokinetic.

pharmacodynamic plasma glucose model to describe the genomic effects of methylprednisolone on PEPCK was developed by Jin et al.^[194] Methylprednisolone was administered to adrenalectomized rats, and liver weights, concentrations of cyclic adenosine monophosphate (cAMP), PEPCK messenger RNA (mRNA) and PEPCK activity were measured. Among other complexities, the model includes the interaction between methylprednisolone and its receptor. The nuclear drug-receptor complex stimulates production of PEPCK mRNA, which is described by IDR model III and results in higher PEPCK activity. The drug-receptor complex also inhibits degradation of cAMP, which further stimulates PEPCK activity. For model evaluation, the simulated profiles from the established model were compared with data from a validation study, and good agreement was reported. As PEPCK increases glucose production, this model can be combined with the glucose-insulin feedback model by Lima et al.^[103] discussed in sections 4.2 and 6. Due to the complexity of the model, a piecewise fitting technique was used, and parameters that were estimated first were fixed in the subsequent steps of data analysis.^[194] With the growing possibilities of measuring more endogenous substances that are potentially important for drug action, more of these systems biology types of models will evolve.

8. Models for Disease Progression

In the models that have been discussed so far, it was assumed that the disease status is constant over the whole observation period of the study. As diabetes is a chronic progressive disease, this assumption is not realistic for long-term studies. In addition, the efforts in development of new diabetic agents are directed towards drugs that can alter disease progression. Therefore, it is particularly important to include disease progression in models for long-term studies with antidiabetic agents. Changes in disease status also need to be included in simulations of long-term clinical trials. After a disease progression model has been established for a specific patient population, the disease progression can be predicted for other patients with characteristics similar to those of the population that was studied. Disease progression models are also needed to quantify the drug effect independently of the disease progression. Disease progression modelling was listed in the critical path opportunity list by the US FDA in 2004.^[204]

The state of a patient is influenced by both the disease and the drug action. Therefore, clinical pharmacology has been described as the combination of the disease progress and drug action.^[205] A disease progression model describes the changes in the patient status over time in the absence of the investigated drug. Ideally, data from a placebo or untreated group should be available; however, for ethical reasons, this is often not feasible. An example of a long-term study of diabetes in which the natural disease history without drug treatment was investigated is the Belfast Diet Study.^[206]

Disease progression modelling has been reviewed previously.^[205,207,208] Drug effects were characterized as 'symptomatic' or 'disease modifying'. A symptomatic drug effect ameliorates the disease state only while the drug is given, but the rate of disease progression is the same as without treatment. When the drug is discontinued, the disease status will be the same as if no drug had been given. Linear models describe disease progression with a baseline and a slope. A symptomatic drug effect can be described by a change in baseline when the drug is started. A disease-modifying effect changes the rate of the disease progression, and the progression can be slowed down or stopped.

Few authors have modelled disease progression of diabetes. In 2003, Frey et al.^[146] developed a population model for the effect of sustained-release gliclazide on FPG in 634 T2DM patients over 10 weeks or 1 year. In patients responding to the treatment, FPG levels initially declined and then slowly increased again. In non-responders, FPG levels increased without the initial decline. The change in FPG levels over time was described by an empirical linear model with an intercept and positive slope (equation 3):

$$\text{FPG}_t = \text{Baseline} + \alpha \cdot t - E_t \quad (\text{Eq. 3})$$

where FPG_t is the predicted FPG at time t , Baseline is the predicted FPG at baseline, α is the slope of the disease progression and E_t is the predicted treatment effect at time t .

Gliclazide was assumed to have no disease-modifying effect, and no dose adjustment was made during the 6-month maintenance period of the study. Therefore, the slope α represented the rate of disease progression and was estimated at 0.84 mmol/L/year, with a large interpatient variability (coefficient of variation 143%). The symptomatic glucose-lowering effect (E_t) was described by a Hill equation driven by the AUC of the drug in an effect compartment. A mixture model was applied to distinguish between responders and nonresponders. In nonresponders, FPG was described only by the disease progression model without a drug effect E_t . For model evaluation, it was shown that FPG profiles of 232 patients receiving immediate-release gliclazide and not used for model building could be adequately predicted from the model.^[146] This empirical model with linear disease progression could describe the data available for up to 1 year. Linear disease progression models are often most useful for studies of a short duration. Often the rate of disease progression does not stay constant over time but slows down when the disease becomes more severe, and an asymptotic function can better describe the disease progression. If the disease progression is asymptotic and a linear equation from a relatively short study is used to predict longer timeframes, this can result in overestimation of the rate of disease progression.^[208] Frey et al.^[146] included intersubject variability. This is important, as patients usually do not all have the same disease severity when they enter the study, and the rate of

disease progression can differ between individuals. As insulin concentrations were not available, the mechanism of action of gliclazide, which is stimulation of insulin secretion, could not be described by the model. Moreover, HbA_{1c} concentrations as a more long-term marker for disease status were not available.

Recently, Post et al.^[109] proposed a family of mechanism-based disease progression models that describe disease as a disturbance of homeostasis based on an IDR model. In this framework, disease alters the k_{in} or k_{out} of an endogenous substance in a time-dependent manner. This approach requires some knowledge about the underlying mechanism of the disease. The same group applied this approach to model disease progression in T2DM.^[109] Data from two 1-year studies in 2408 treatment-naïve T2DM patients were modelled utilizing the population approach. The glucose-insulin-HbA_{1c} system and the drug effects were described as discussed in sections 4.2 and 5.3 (see figure 5). Disease progression was described as a decrease in both β -cell function and insulin sensitivity, and was included in the model by the terms B and S (figure 5). B describes the remaining fraction of β -cell function and S describes the remaining fraction of insulin sensitivity in diabetic patients compared with healthy subjects. The B and S correspond to HOMA-B and HOMA-S (see section 4.1) calculated by the HOMA1 approximation. The changes in β -cell function and insulin sensitivity over time were described by an empirical exponential function (figure 5). The parameters b_0 and s_0 describe the initial condition of the disease progression curves, and r_B and r_S describe the slopes of the disease progression curves. B is included in the equation that describes fasting serum insulin, such that a decrease in B decreases insulin production. Decreasing S increases glucose production and vice versa. Drugs that have disease-modifying effects influence the slope of the disease progression. To investigate the disease-modifying effects of pioglitazone and metformin on β -cell function and insulin sensitivity, r_B and r_S were estimated for each treatment group. As in the model of Frey et al.,^[146] gliclazide was assumed to have no disease-modifying effect. In addition, symptomatic drug effects on β -cell function (EF_B) and insulin sensitivity (EF_S) were included. Whereas changes in r_B and r_S due to drug treatment influence the disease progression, EF_B and EF_S describe an offset in the disease status, which immediately disappears after drug treatment is stopped. In this model, only hepatic insulin sensitivity is considered. Visual predictive checks, the objective function in NONMEM and the Akaike information criterion were used for model evaluation.

From their model, de Winter et al.^[109] found disease-modifying effects of metformin on β -cell function and of pioglitazone on both β -cell function and insulin sensitivity. According to the authors, the apparent disease-modifying effect of metformin on β -cell function is due to model misspecification of the mechanism of action of metformin, and not due to a true improvement. For the symptomatic effects, it was assumed that gliclazide had an effect

on β -cell function and that metformin and pioglitazone affected insulin sensitivity. The authors reported that the effect of gliclazide was probably artificially inflated because of model over-prediction.

The increase in FPG was seemingly linear, although composed from two asymptotic functions for B and S. The rate of FPG increase was similar, about 1.0 mmol/L/y in the model by de Winter et al.^[109] and about 1.2 mmol/L/y when the model by Frey et al.^[146] was applied to the data from de Winter et al.^[109]

Overall, the model has some important advantages. It includes the interactions of glucose, insulin and HbA_{1c} and also the effects of drugs with different mechanisms of action. It distinguishes between symptomatic and disease-modifying drug effects on glucose and insulin production. Disease progression was described as a change in β -cell function and insulin sensitivity. As for the limitations of their study, the authors stated that no placebo group and no off-response (where final samples are taken after the end of the treatment and a washout phase) were available.^[109] Moreover, pharmacokinetic data were not available. The authors reported model misspecification for metformin. The predicted decrease in insulin sensitivity over time for all drugs was in contrast to the findings from ADOPT (A Diabetes Outcome Progression Trial)^[210] in recently diagnosed T2DM patients, where insulin sensitivity (HOMA-S) increased under treatment with rosiglitazone and metformin and was constant or insignificantly increased during glibenclamide treatment. As the equations for B and S were empirical asymptotic functions, extrapolation of these equations to 10 years, as was done in the article, should be interpreted with caution.

Topp et al.^[211] proposed a model for glucose, insulin and β -cell mass. It is assumed that a gradual increase in glucose concentrations results in growth of β -cell mass, whereas severe hyperglycaemia leads to a decrease of β -cell mass, e.g. due to pancreatic exhaustion or glucotoxicity. Therefore, it is suggested that β -cell failure is due to persistent hyperglycaemia. These assumptions were based on *in vitro* experiments. The model consists of three differential equations, one each for glucose, insulin and β -cell mass. The parameter values for the normal human physiological state were taken from the literature. By use of this model, three pathways that can lead to overt diabetes were simulated. However, no model fittings to real data were shown. Recently, Hamrén^[212] described an extension of the model by Topp et al.^[211] The effects of tesaglitazar on β -cell mass and insulin sensitivity and a positive relation of insulin sensitivity with insulin clearance were added. This model was combined with the previously developed pharmacokinetic/pharmacodynamic model for the effects of tesaglitazar on FPG, FSI, haemoglobin and HbA_{1c}^[166] (see section 5.3) and applied to clinical data. Model predictions were shown for β -cell mass and insulin sensitivity.

Bagust and Beale^[213] used the results of the Belfast Diet Study^[206] to develop an empirical model for the decay of β -cell function over time. In the Belfast Diet Study, newly diagnosed T2DM patients who were managed on diet alone were followed-up over 6 years. The β -cell function data over 6 years were fitted to a two-part spline function describing a slow loss of β -cell function for a long time period followed by a rapid decay phase. It was assumed that the patients were diagnosed at different stages of the disease. Their results suggested that the time to failure of dietary treatment mainly depends on the time from the onset of diabetes. This model is empirical but shows that disease progression was not constant over time and that the shape of the disease progression curve depends on the point on the disease pathway at which a newly presenting patient is located. The authors compared the decline of β -cell function per year to the decline that was reported from the UKPDS (UK Prospective Diabetes Study). The decline in β -cell function in the UKPDS interim results was 9.5% per year, which was midway between the two decline phases in the model by Bagust and Beale.^[213] In contrast to de Winter et al.,^[109] Bagust and Beale^[213] and Topp et al.^[211] assumed that the only underlying reason for disease progression in diabetes is loss of β -cell function. This assumption was supported by previous reports. Both insulin resistance and insufficient β -cell function are important in the pathology of diabetes.^[2] However, insulin resistance can be compensated for by hyperinsulinaemia. β -cell function decreases over time and, because of this decline, T2DM develops.^[2]

Several types of model were developed for long-term disease progression and drug effects.^[214] These include regression models (e.g. the Framingham risk score for myocardial infarction)^[215] and Markov models (e.g. the Global Diabetes Model).^[216] However, these models do not take into account the underlying mechanism and pathophysiology of the disease.

Diabetes is a multifactorial and multiorgan disease. Recently, whole-body simulation models have been developed that include submodels for several different tissues and organs that are important in diabetes. From these models, virtual patients are simulated and the outcomes of clinical trials are predicted. Whole-body simulation models include a large number of compartments and equations and complex mathematics. Therefore, it can be difficult to understand how the model is built, what assumptions are made, and if the model reflects the physiological situation. These models are currently proprietary, and the equations have not been published. The parameter values are taken from the literature. Examples of whole-body simulation models are the Archimedes model,^[217, 218] which was not specifically developed for diabetes, and the Entelos Metabolism and T1DM PhysioLab® platforms.^[219, 220] The Archimedes model was evaluated by predicting the outcomes of 18 different clinical trials, which gave 74 evaluations in total, and in 71 of these, there were no statistically significant differences between the model predictions and the

outcome of the real trials.^[218] Herman^[221] pointed out the lack of transparency and the values of the variables in the Archimedes model as limitations. The general mathematical formulation of the Archimedes model has been published.^[222] Apart from the physiological part of the model, the Archimedes model also includes a model of care processes, including the costs of therapy. Whole-body simulation models could be used to predict disease progression in diabetic patients and may help to reduce the number of clinical trials that need to be performed to study drug effects, which is both ethically and financially advantageous. The attrition rate for antidiabetic drugs might be decreased or the decision could be made earlier, if the drug effects in humans can be predicted by use of a model and, for example, data from *in vitro* or animal studies.

Various long-term models for estimation of the cost-utility of antidiabetic treatments have been proposed. A comparison of eight long-term simulation models, including validation against real clinical trials, has been reported by the Mount Hood 4 Modelling Group.^[223] Guidelines for modelling or predicting the outcomes of long-term diabetes trials have been developed by the ADA.^[224] The ADA consensus panel underlines the importance of model transparency, validation (evaluation) and assessment of uncertainty. Several special requirements, such as accounting for long-term complications, multiple organ systems and multidrug therapy, have been pointed out.

9. Future Needs and Perspectives

Many models have been developed to describe the glucose-insulin system. Fewer models are available that quantify drug effects, which is the primary focus of this review. Compared with models published in pharmacological journals, models published in mathematical or statistical journals are often more detailed and are usually based on more complex mathematics. However, in the latter models, drug effects are usually not included, and the model predictions are most often not compared with real data. Moreover, they often consist of many equations and a large number of parameters that cannot be estimated from clinical trial data. These models are suitable for simulation of complex systems. For estimation, the models should ideally be relatively simple and include the most important parts that are needed to describe the drug action, the glucose-insulin system and disease progression. The models need to be evaluated against real clinical data in order to assess their predictive performance and clinical utility.

Overall, many models have been developed for different purposes. Depending on the problem that needs to be solved, the advantages and limitations of the available models should be considered, and the model that best applies to the problem can be chosen. Although a large number of models are available, some needs that should be addressed in the future have been identified.

As it is the centre of the glucose-insulin system, the reciprocal feedback between glucose and insulin should be included more often in the models, although it represents a modelling difficulty. It would therefore be important for insulin data to be available from the studies, including long-term studies. As the action of insulin and some antidiabetic drugs on glucose depends on the dietary situation (i.e. the fasting or postprandial state), this should be taken into account in the model. For some drugs or drug groups such as pramlintide, DPP-4 inhibitors and α -glucosidase inhibitors, mechanism-based models are not yet available. In the context of evaluating long-term drug effects, it is important to substantiate disease progression and identify biomarkers or new targets for long-term effects. In order to better understand the underlying pathophysiology of diabetes, study of the time course of genetic factors is needed. To support drug development, models that describe similarities and differences in antidiabetic drug effects between animal studies and human studies are needed to allow for translation of drug effects. An ultimate goal is to include the glucose-insulin system, disease progression, and the pharmacokinetics and effect of a drug in the same model. Depending on the goal of the modelling and the drug that is studied, the most important subsystems should be identified so that the model does not become too complex and maybe inestimable, but still includes the major components that are important to describe the drug action and effects. In the same context, identification of appropriate model simplifications is desirable. Frequently, diabetic patients are treated using multidrug therapy. For these cases, models that can describe the interactions and possible synergisms between different antidiabetic drugs on a mechanistic basis are needed.

10. Conclusions

A large number of models for various purposes have been proposed in the context of diabetes, and the need for mechanism-based models in diabetes has been recognized. Whereas most of the published models focus on the glucose-insulin system or important subsystems, fewer models are available that describe the effects of antidiabetic drugs. Modelling of drug effects has mostly used biophase models or IDR models. IDR models can often describe drug effects more mechanistically and can also describe disease progression. The choice of a model from the large number available depends on the purpose of the study, as models for various purposes are available. Future needs are to more often include the reciprocal glucose-insulin feedback, develop mechanistic models for new drug groups and consider dual drug effects on complementary subsystems. Further goals are to include elements of disease progression and to identify and model new and predictive biomarkers.

Acknowledgements

The authors thank Drs Richard Almon and Debra DuBois for their critical review of the manuscript and valuable comments, and Prof. Amanda Almon for preparing the illustrations for figures 1 and 2. This work was supported by the UB-Pfizer Strategic Alliance. The authors have no conflicts of interest that are directly relevant to the content of this review.

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