Development of Disease Progression Model in Korean Patients with Type 2 Diabetes Mellitus

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Development of Disease Progression Model in Korean Patients with Type 2 Diabetes Mellitus

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2012년 6월

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ABSTRACT

Development of Disease Progression Model in Korean Patients with Type 2 Diabetes Mellitus

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Type 2 diabetes mellitus (T2DM) is a progressive disease. Decline in β-cell function, increase in insulin resistance with concomitant increase in fasting plasma glucose are the natural sequelae of T2DM. Although some pharmacotherapies for patients

with type 2 diabetes mellitus have shown to slow the rate of progression or improve disease status, none of them has been proven to halt disease progression. Nevertheless, based on meta-analysis of existing data, it is hoped that more intensive treatment compared to standard glycemic control would significantly reduce coronary events without a parallel increase in mortality and morbidity. In such regards, disease progression of T2DM might be controlled by adopting proper treatment strategies. Pharmacometrics is a cutting-edge area of clinical pharmacology which is defined as the science that quantifies drug action, disease progression and patient information to aid efficient drug development, regulatory decision, and treatment in actual clinical practice. A disease model, represented by baseline disease status, natural disease history and drug (and placebo) response, describes the time course of disease progression, as measured by biomarkers or clinical outcomes, segregated from the drug response. The purpose of this study is to develop a disease progression model for Korean patients with T2DM and to apply the developed model as a supportive tool to designing an optimal treatment regimen in this clinical population using NONMEM.

A total of 347 new or established patients who visited Severance hospital for the first time from 2006 to 2012 were retrospectively investigated after screening 888 patients. The patients were prescribed 0 to 3 kinds of oral hypoglycemic agents (OHAs) at first visit according to their disease status by endocrinology specialists. The primary endpoints measured were fasting plasma glucose (FPG, mmol/L) and glycated hemoglobin (HbA1c, %). We performed the analyses according to the intention-to-treat principle. Disease progression was modeled using the natural

history and drug effect influencing the baseline ("offset") or the progress rate ("slope"), or both. The constant, linear, simple E_{max}, sigmoid E_{max} and power models were evaluated to describe the treatment effect. The concept of effect compartment was applied to explain the delay in time course between pharmacokinetic steady state and pharmacodynamic steady state. The number of OHAs was incorporated into the structural model. Next, stepwise covariate model building was performed. The relationship between the structural parameters and the classes of the OHAs were investigated in this step. The final model was evaluated by the visual predictive check (VPC) for 1000 simulations.

The median age of eligible patients (185 males, 162 females) was 61 years (19 – 85). Metformin was most frequently prescribed followed by sulfornylureas. The greater the number of OHA classes prescribed, the faster were the dropout rates. The number of patients without drug prescription was 19 and these patients were excluded from the population analysis because they were not suitable candidates for a placebo effect group. A total of 328 patients were prescribed 1 to 3 classes of OHAs. The number of OHAs positively correlated with the level of FPG or HbA1c acquired from initial laboratory tests. Linear models for offset effect and constant model for slope effect were incorporated into the final disease progression model for FPG and HbA1c.

FPG and HbA1c increased naturally 0.197 mmol/L/year (3.55 mg/dL/year) and 0.181%/year, respectively. The amplitude of offset effect increased with the number of prescribed drugs in both FPG and Hb1Ac, though for HbA1c, there were little differences between 2 drugs and 3 drugs. The equilibration half-lives for offset

effect were 14 days and 35 days for FPG and HbA1c, respectively. Therefore, it took around 55 to 69 days and 140 to 175 days for FPG and HbA1c, respectively to reach pharmacokinetic and pharmacodynamic equilibrium state.

The disease progression rates of the Korean patients with type 2 diabetes mellitus who visited Severance hospital were similar to those of western patients, with rates for fasting plasma glucose and glycated hemoglobin 0.039 to 0.31 mmol/L and 0.07 to 0.24 %/L, respectively. Fasting plasma glucose decreased faster than glycated hemoglobin at the beginning of treatment. Treatment effect decreased inversely proportional to diabetes duration. The greater the number of prescribed drugs, the bigger was the offset effect. I will build disease progression model with greater utility after undertaking further studies.

Key words: type 2 diabetes mellitus, disease progression model, fasting plasma glucose, glycated hemoglobin, quantitative analysis, population analysis

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I. INTRODUCTION

1. Type 2 Diabetes Mellitus

Type 2 diabetes mellitus (T2DM) is a progressive disease. Decline in β-cell function, increase in insulin resistance with concomitant increase in fasting plasma glucose (FPG) are the natural sequelae of T2DM.[1,2] (Figure 1) In many cases, T2DM results in fatal or nonfatal macrovascular (myocardial infarction, angina, stroke), microvascular (nephropathy, retinopathy) and peripheral vascular(amputation, death) diseases.

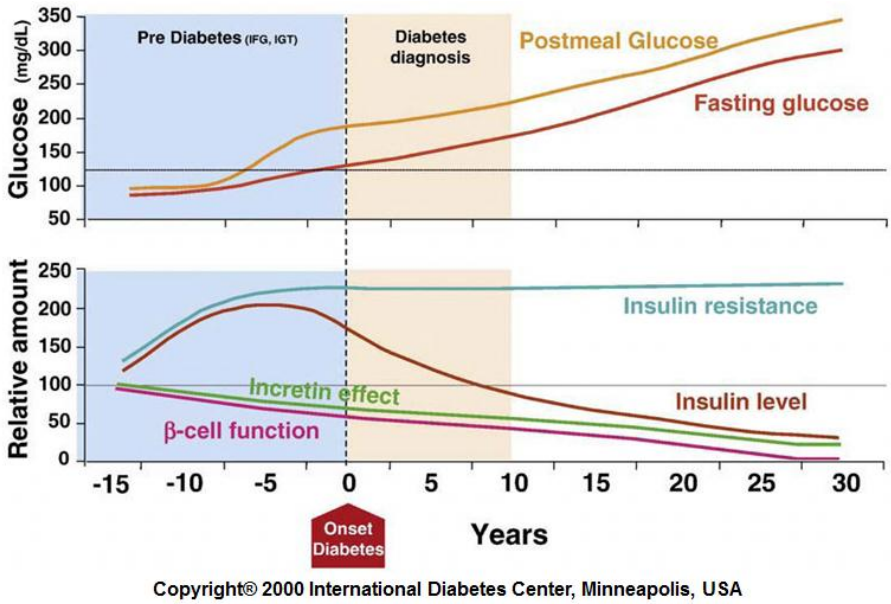

Figure 1. Natural History of Type 2 Diabetes

Although some pharmacotherapies for patients with type 2 diabetes mellitus have shown to slow the rate of progression or improve disease status, none of them has

been proven to halt disease progression. When rosiglitazone, metformin and glyburide were given to patients, the mean level of HbA1c (Panel B) and FPG (Panel A) started to rise again after brief drops while β-cell function (Panel D) showed just the opposite trend. Only insulin sensitivity (Panel C) improved during treatment.[3] (Figure 2)

Nevertheless, it is hoped that more intensive treatment compared to standard glycemic control would significantly reduce coronary events without a parallel increase in mortality and morbidity, based on meta-analyses including United Kingdom Prospective Diabetes Study (UKPDS), PROspective pioglitazone Clinical Trial In macroVascular Events (PROactive), Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE), Veterans Affairs Diabetes Trial (VADT), and Action to Control Cardiovascular Risk in Diabetes trial (ACCORD).[4] Some classes of OHAs such as biguanide, thiazolidinedione and exenatide were recently demonstrated to stave off disease progression or to preserve or improve β-cell function.[3,5,6] There are also some encouraging reports of successful intensive treatments with biguanide and thiazolidinedione, with preservation of β-cell function, slowing of disease progression, and reduction of relative risks of the diabetes-related end points, death and microvascular complications.[4,7-13] Therefore, formal understanding of the disease progression of T2DM using a quantitative approach would be an important factor for establishing proper treatment strategies.

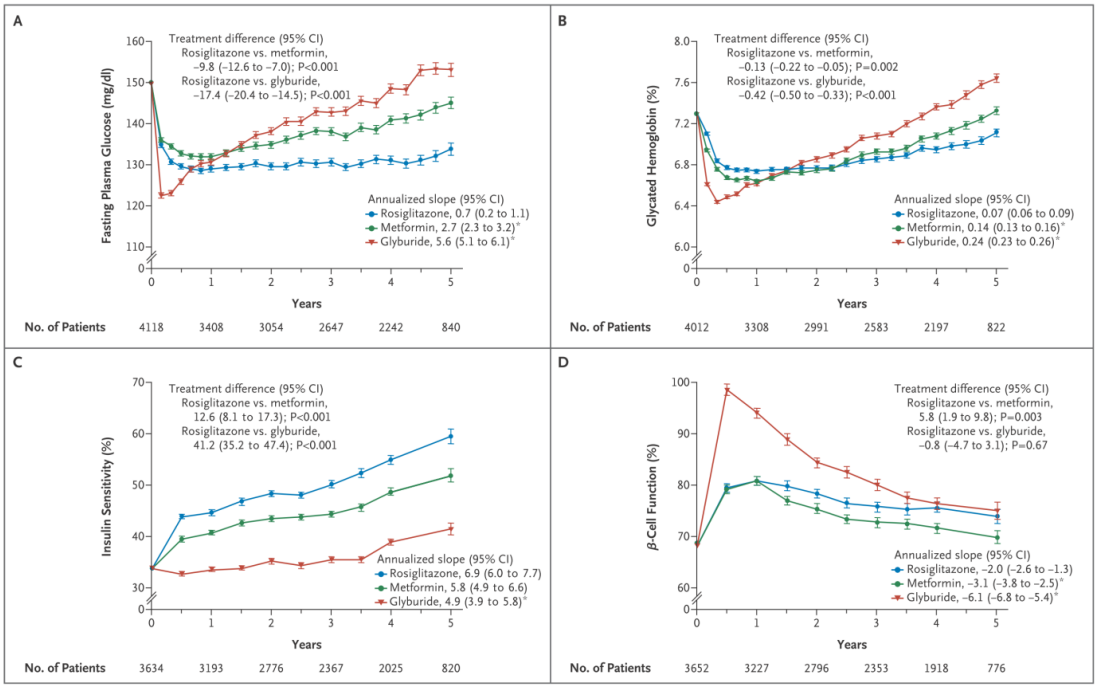

Figure 2. Fasting Plasma Glucose (Panel A), Glycated Hemoglobin (Panel B), Insulin Sensitivity (Panel C) and β-Cell Function (Panel D) over Time, According to Treatment Group

2. The Significance of the Disease Progression Model in Drug Development

Applying model-based approaches, pharmacometrics has been a great help to efficient drug development and evidence based drug treatment.[14] Pharmacometrics is a cutting-edge area of clinical pharmacology which is defined as the science that quantifies drug action, disease progression and patient information to aid efficient

drug development, regulatory decision, and treatment in actual clinical practice. It is now recognized as a core technology in drug development, which has been largely dependent on simple testing of hypotheses so far.

Despite such important progress and contribution to drug development, it is not until recent years that pharmacometrics has come to play an important role in quantitatively understanding characteristics of disease progression using "disease model" or "disease progression model". Many clinicians have empirically evaluated disease status or progression until now.

A disease model, represented by baseline disease status, natural disease history and drug (and placebo) response, describes the time course of disease progression, as measured by biomarkers or clinical outcomes, segregated from the drug response. Recently, a disease model has been recommended by the FDA's critical path document as a potentially valuable tool to improve the predictability and productivity of the drug development process. Moreover, the division of Pharmacometrics at FDA is aiming to develop disease models in several major disease areas and to create public disease model libraries until 2020. Disease progression models are increasingly being applied to various degenerative diseases such as Alzheimer's, Parkinson's, osteoporosis as well as type 2 diabetes mellitus.[15-18] The usefulness of disease progression models is gaining recognition not only from the pharmaceutical industry but also from clinicians. With this regard, a disease progression model for Korean patients with type 2 diabetes mellitus is expected to be a valuable tool to the progression of this disease and an optimal

treatment scheme in this group of Korean patients.

Among computer programs currently available for pharmacometrics analyses, NONMEM (the acronym of Nonlinear Mixed Effects Modeling) has been the most widely used so far, which is also used in this thesis to develop disease models. Here, mixed effects mean fixed and random effects, with the former being the typical parameters common to all individuals (e.g., the average drug clearance) and prognostic factors (e.g., covariates such as age, sex, weight, etc), and the latter being the inter-individual variability, accounting for parameter variations in individuals with the same covariate values.

3. The Development of the Disease Progression Models

A disease progression model can be expressed as the following equation:

$$S(t) = S_0 + Natural\ History + Placebo\ Effect + Active\ Drug\ Effect \quad \text{(Eq. 1)}$$

where S(t) and S_0 represent time course of disease status and the initial or baseline disease status, respectively. Natural history can be interpreted as any change from baseline status unaffected by medical treatments, including placebo. The drug effect could be divided into placebo effect and active drug effect under different circumstances.

The following linear equation is the simplest disease progression model.

$$S(t) = S_0 + \alpha \times t \quad \text{(Eq. 3)}$$

This represents progression of disease status with constant rate (slope α) over time.

Since treatment effects change disease status over time, equation 3 can be modified to:

$$S(t) = S_0 + E_{SYM}(t) + \alpha \times t \quad \text{(Eq. 4)}$$

where $E_{SYM}(t)$ represents a treatment effect that gives a temporary improvement (offset) in the disease status during treatment. However, if treatments are discontinued, the effect washes out and disease status returns to the untreated status. This is called symptomatic effect (offset effect).[18,19] (Figure 3)

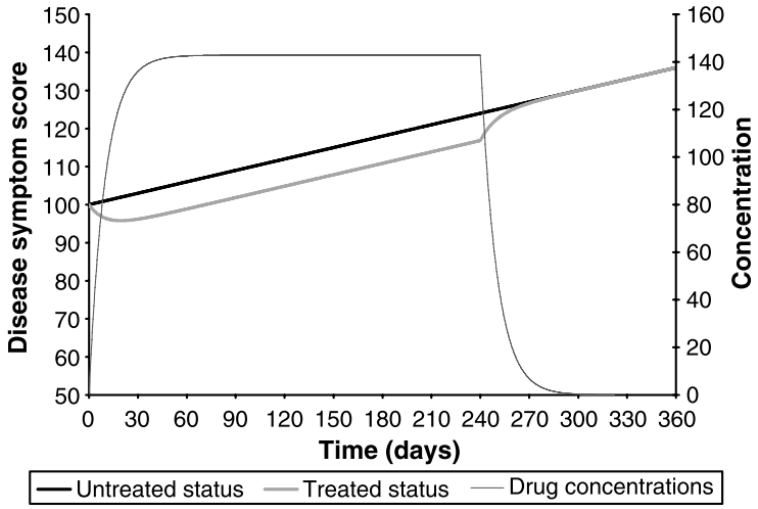

Figure 3. Symptomatic treatment effect on the progression of disease.

On the other hand, treatment effect might change the progression of disease:

$$S(t) = S_0 + (E_{MOD}(t) + \alpha) \times t \quad \text{(Eq. 5)}$$

where $E_{MOD}(t)$ represents a treatment effect modifying the rate of disease progression (slope α). Under such circumstances, even when the treatments are discontinued, the effect does not wash out and the disease status does not return to the untreated natural status but results in a permanent improvement. This is called disease modifying effect (slope effect).[18,19] (Figure 4)

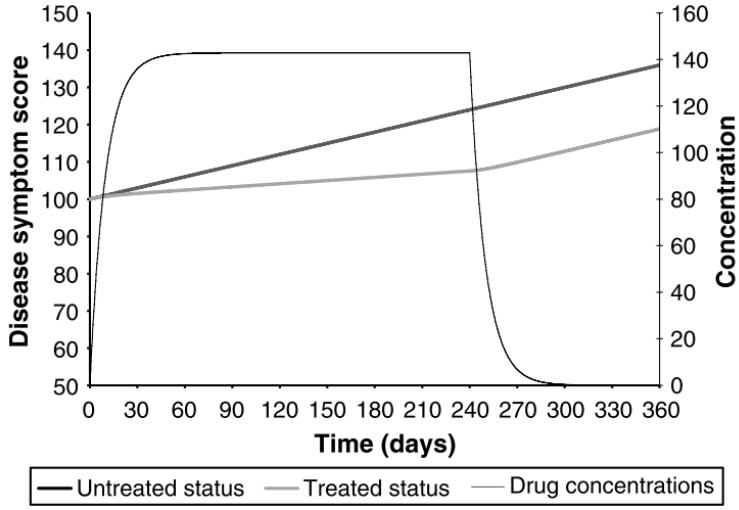

Figure 4. Disease modifying treatment effect on the progression of disease.

4. Purpose

The purpose of this study is to develop a disease progression model for Korean patients with T2DM and to apply the developed model as a supportive tool to designing an optimal treatment regimen in this clinical population.

II. METHODS

1. The Patients with Type 2 Diabetes Mellitus

A total of 347 patients who visited Severance hospital for the first time from 2006 to 2012 were retrospectively investigated after screening 888 patients. A total of 541 patients were excluded due to following conditions: dropout after the first visit, only one laboratory test taken, previous experience of insulin therapy, and insufficient records. The patients were prescribed 0 to 3 kinds of oral hypoglycemic agents at the first visit according to their disease status by endocrinology specialists. The data of the patients after prescription was changed from the initial prescription were excluded from the analysis. The primary endpoints measured were fasting plasma glucose (FPG, mmol/L) and glycated hemoglobin (HbA1c, %). The following laboratory tests were additionally performed: Insulin, C-peptide, total cholesterol, triglyceride, high density lipoprotein cholesterol, low density lipoprotein cholesterol, C-reactive protein, BUN, creatinine, hematocrit, hemoglobin, aspartate-aminotransferase, alanine-aminotransferase, albumin creatinine ratio. The demographic factors investigated at first treatment were weight, height, circumference of hip and waist, past history, family history, smoking history and alcohol history. Comorbidities related to type 2 diabetes mellitus were checked: macrovascular disease (coronary artery disease, stroke), microvascular disease (nephropathy, retinopathy) and diabetic neuropathy. Other comorbidities such as hypertension, B/C viral hepatitis, pulmonary tuberculosis and cancer were also looked into. Demographic factors were analyzed using parametric statistical

analyses (t-test, ANOVA, etc.) and non-parametric statistical analyses: Wilcoxon signed rank test, Wilcoxon rank-sum test, chi-squared test, etc.)

2. Disease Progression Model

A. Structural Model Building

(1) Disease Progression Model

I performed the analyses according to the intention-to-treat principle. Disease progression was modeled using natural history, denoted by the baseline (S_0), progress rate (α), and drug effect influencing the baseline ("offset") or the progress rate ("slope"), or both.

Model 1: $\mathrm{S(t)} = S_0 - E_{SYM}(t) + \alpha \times t$

Model 2: $\mathrm{S(t)} = S_0 + (\alpha - E_{MOD}(t)) \times t$

Model 3: $\mathrm{S(t)} = S_0 - E_{SYM}(t) + (\alpha - E_{MOD}(t)) \times t$

(2) Drug Effect Model

The following constant linear, simple E_{max} and sigmoid E_{max} models were evaluated to describe the treatment effect.

Constant model: $E(t) = \beta$

Linear model: $E(t) = \beta \times DE(t)$

Simple E_{max} model: $E(t) = \frac{E_{max} \times DE(t)}{ED_{50} + DE(t)}$

Sigmoid E_{max} model: $E(t) = \frac{E_{max}^{\gamma} \times DE(t)^{\gamma}}{ED_{50}^{\gamma} + DE(t)^{\gamma}}$

Power model: $E(t) = \beta^{\gamma} \times DE(t)$

β represents the slope of linear model, E_{max} the maximum drug effect, ED_{50} the effect site dose that produce half maximum drug effect, γ the steepness parameter, and DE(t) the effect site dose.

The concept of effect compartment was applied to explain the delay in time course between pharmacokinetic steady state and pharmacodynamics steady state:

$$DE(t) = Dose \times (1 - e^{-K_{eq} \times t})$$

where K_{eq} is the rate constant of equilibration between the two states.[20,21]

For each of the above model parameters, the inter-individual variability was defined as follows:

$$P = \theta_P \bullet \exp(\eta_P)$$

where P is the individual value of model parameter, θ_P is the population-average value of model parameter, and η_P is the inter-individual difference, normally distributed with mean zero and variance ω_p^2.

The number of drug classes was incorporated into the basic model building to reflect drug effects by assign different typical parameters according to the number.

B. Covariate Model Building

After the visual inspection of the relationships between covariates and the empirical Bayes estimates (EBEs) of the basic model parameters obtained at the previous stage above, stepwise covariate modeling (SCM) using the PsN software was performed (Perl-speaks-NONMEM, version 3.4.2, http://psn.sourceforge. net).[22] The likelihood ratio test (LRT) was used to select significant covariates, with the significance levels of $p < 0.01$ for forward selection and $p < 0.001$ for backward elimination. The relationship between the structural parameter and the classes of the OHAs such as biguanide (BID), sulfornylurea (SUL), thiazolidinedione (TDZ), maglitinide (MAG), α-glucosidase inhibitor (AGS) and DPP-4 inhibitor (DPP) were evaluated in this step. The following covariates were tested: age, body mass index, weight, height, circumference of hipand waist and waist to hip ratio for continuous covariates, and gender for dichotomous covariates. Whether or not patients had family history, smoking history, alcohol history, macrovascular disease, microvascular disease or diabetic neuropathy was also tested as dichotomous

covariates. Diabetic complications, like nephropathy, retinopathy and neuropathy and co-morbidities, such as cardiovascular disease, cerebrovascular disease, hepatic disease, renal disease, hypertension, hypercholesterolemia, cancer, carotid artery atherosclerosis were also reflected in the covariate analysis. The measured levels of pre- and post-prandial insulin and C-peptide, blood urea nitrogen, creatinine, low density lipoprotein cholesterol, triglyceride, high density lipoprotein cholesterol, total cholesterol, and hemoglobin at diagnosis were also explored.

C. Model Evaluation

The final model was evaluated by the visual predictive check (VPC) for 1000 simulations performed using the PsN tool (Perl-speaks-NONMEM, version 3.4.2, http://psn.sourceforge.net).

D. Analysis Software

All analyses described in the Methods section were performed using NONMEM (version 7.2, ICON Development Solutions, Ellicott City, MD, USA) was used. All the plots were created using R (http://www.r-project.org).

III. RESULTS

1. Data for the Patients with Type 2 Diabetes Mellitus

The median age of eligible patients (185 males, 162 females) was 61 years (19 – 85). The dichotomous demographic factors are shown in Table 1. 19 patients visited to receive the check without outpatient prescription. Smokers and ex-smokers constituted 28% of the total patients and the number of male overwhelmed that of female. Patients who had drinking history constituted 25% of the total subjects. Patients with a family history of diabetes were 21% of the total. Most common comorbidities were hypertension (58%) followed by hypercholesterolemia (38%). In addition, cancer (19%), liver disease (16%), cardiovascular disease (13%) and cerebrovascular disease (11%) were often accompanied. 15% of the patients were diagnosed with carotid artery atherosclerosis and 17% had complication of diabetes. (Table 1)

Table 1. Dichotomous Demographic Factors

	Total			Male			Female		
Demographic Factors	Number	No (%)	Yes (%)	Number	No (%)	Yes (%)	Number	No (%)	Yes (%)
Medication	347	19 (5%)	328 (95%)	185	14 (8%)	171 (92%)	162	5 (3%)	157 (97%)
Smoking	306	220 (72%)	86 (28%)	165	84 (51%)	81 (49%)	141	136 (96%)	5 (4%)
Alcohol	306	229 (75%)	77 (25%)	165	94 (57%)	71 (43%)	141	135 (96%)	6 (4%)
Family History	320	253 (79%)	67 (21%)	170	135 (79%)	35 (21%)	150	118 (79%)	32 (21%)
Hypertension	338	143 (42%)	195 (58%)	178	78 (44%)	100 (56%)	160	65 (41%)	95 (59%)
Liver Disease	339	284 (84%)	55 (16%)	180	151 (84%)	29 (16%)	159	133 (84%)	26 (16%)
Renal Disease	336	322 (96%)	14 (4%)	178	167 (94%)	11 (6%)	158	155 (98%)	3 (2%)
Cardio Vascular Disease	336	294	42	178	149	29	158	145	13

		(88%)	(13%)		(84%)	(16%)		(92%)	(8%)
Cerebro Vascular Disease	335	299	36	177	158	19	158	141	17
		(89%)	(11%)		(89%)	(11%)		(89%)	(11%)
Cancer	334	272	62	177	145	32	157	127	30
		(81%)	(19%)		(82%)	(18%)		(81%)	(19%)
Hypercholesterolemia	340	211	129	179	119	60	161	92	69
		(62%)	(38%)		(66%)	(34%)		(57%)	(43%)
Diabetic Complication	337	292	45	179	158	21	158	134	24
		(87%)	(13%)		(88%)	(12%)		(85%)	(15%)
Carotid Artery Atherosclerosis	337	280	57	179	150	29	158	130	28
		(83%)	(17%)		(84%)	(16%)		(82%)	(18%)

The continuous demographic factors are shown in Table 2. The median disease duration was 2.5 years and varied from 0 to 40. The median BMI was 25.5, which were marginally overweight. The median WHR, a significant predictor of diabetes, was above 0.9. The median levels of preprandial c-peptide, postprandial c-peptide, prepandial insulin, and postprandial insulin were mostly in the normal range, which were unexpected. The median lipid profiles were also normal, probably because patients with hypercholesterolemia were prescribed lipid-lowering agents. (Table 2)

Table 2. Continuous Demographic Factors

Demographic Factors	Total			Male			Female		
	Number	Mean (SD)	Median (Range)	Number	Mean (SD)	Median (Range)	Number	Mean (SD)	Median (Range)
Age (yesr)	347	59.9 (11.2)	61.0 (19.0 – 85.0)	185	58.0 (11.6)	59.0 (30.0- 85.0)	162	62.1 (10.4)	63.0 (19.0 – 84.0)
Diabetes Duration (year)	343	5.10 (7.20)	2.50 (0.00 – 40.0)	183	5.10 (7.93)	1.50 (0 - 40)	160	5.10 (6.29)	3.00 (0.00 – 30.0)
Height (cm)	329	162 (8.81)	162 (135 - 187)	173	168 (6.33)	169 (153 - 187)	156	155 (5.44)	156 (135 - 166)
Weight (Kg)	331	66.5 (11.6)	65.0 (38.0 - 114)	174	71.1 (11.4)	70.0 (48 .0- 114)	157	61.5 (9.64)	61.0 (38.0 – 98.0)
BMI (Kg/m^2)	331	25.5 (4.40)	25.0 (17.4 - 68.4)	174	25.3 (4.50)	24.9 (18.1 - 68.4)	157	25.7 (4.40)	25.3 (17.4 - 58.2)
Waist (cm)	162	88.5 (9.34)	88.0 (65.0 - 119)	84.0	89.1 (9.17)	90.0 (66.0 - 115)	78.0	87.8 (9.54)	87.0 (65.0 - 119)
Hip (cm)	155	95.4 (6.92)	95.0 (74.0 - 125)	80.0	95.1 (6.63)	95.0 (74 .0- 116)	75.0	95.8 (7.25)	96.0 (79.0 - 125)

Waist/Hip Ratio (%)	155	92.5 (6.86)	92.0 (77.7 - 126)	80.0	93.3 (6.76)	92.3 (79.5 - 126)	75.0	91.6 (6.90)	90.3 (77.7 - 109)
Preprandial C-peptide (mg/mL)	237	2.55 (1.06)	2.41 (0.33 - 6.39)	133	2.58 (1.14)	2.41 (0.33 - 6.39)	104	2.51 (0.96)	2.40 (0.94 - 5.93)
Postprandial C-peptide (mg/mL)	227	6.80 (2.86)	6.42 (1.02 – 15.0)	127	7.02 (3.01)	6.53 (1.02 – 15.0)	100	6.52 (2.66)	6.33 (1.89 - 14.9)
Preprandial Insulin (μIU/mL)	151	9.84 (6.14)	8.87 (1.60 - 41.4)	81.0	9.25 (6.40)	8.64 (1.60 - 41.42)	70.0	10.53 (5.78)	9.45 (1.63 - 30.4)
Postprandial Insulin (μIU/mL)	143	49.1 (35.9)	40.7 (2.27 - 188)	77.0	49.7 (38.6)	37.8 (2.27 - 188)	66.0	48.5 (32.7)	42.64 (9.12 - 170)
BUN (mg/mL)	336	16.3 (6.03)	15.0 (5.40 - 56.7)	178	17.0 (6.05)	15.9 (7.00 – 42.0)	158	15.4 (5.91)	14.7 (5.40 - 56.7)
Creatinine (mg/mL)	334	0.96 (0.32)	0.90 (0.50 - 2.88)	176	1.08 (0.31)	1.00 (0.61 - 2.85)	158	0.83 (0.28)	0.78 (0.5 - 2.88)
LDL-cholesterol (mg/mL)	145	112 (33.1)	108 (34.0 - 210)	82.0	110 (35.5)	105 (34.0 - 199)	63.0	114 (29.6)	112 (59.0 - 210)
Triglyceride (mg/mL)	304	158 (114)	130 (33.0 - 1089)	162	172 (137)	130 (37.0 - 1089)	142	142 (79.0)	130 (33.0 - 656)
HDL-cholesterol	299	47.8	46.0	158	45.7	45.0	141	50.2	47.0

(mg/mL)		(12.3)	(11.0 – 98.0)		(11.2)	(11.0 – 83.0)		(13.0)	(26.0 – 98.0)
Total Cholesterol	331	178	175	177	173	169	154	183	182
(mg/mL)		(38.4)	(88.0 - 320)		(39.8)	(88.0 - 320)		(36.1)	(107 - 288)
Hemoglobin (g/mL)	197	13.6	13.7	105	14.2	14.8	92.0	12.9	12.95
		(1.91)	(7.95 - 17.7)		(2.06)	(7.95 - 17.7)		(1.42)	(8.70 - 16.9)

The prescribed drugs are shown in Table 3 sorted by class. Metformin was most frequently prescribed. The patients initially took 0 to 3 classes of medications before the regimen changed.

Table 3. Prescribed Oral Hypoglycemic Agents

Class	Generic name	Trade name	Total (328)
Biguanide	Metformin	Glupa, Diabex	254 (77%)
Sulfornylurea	Glimepiride	Amaryl, Gla-DM	133 (41%)
	Gliclazide	Diamicron	45 (14%)
	Glibenclamide	Gluriad	2 (1%)
Thiazolidinedione	Rosiglitazone	Avandia	40 (12%)
	Pioglitazone	Actos	31 (9%)
Meglitinide	Nateglinide	Fastic	13 (4%)
	Repaglinide	Novo-Norm	2 (1%)
α-Glucosidase inhibitor	Voglibose	Basen	28 (9%)
	Acarbose	Glucobay	12 (4%)
DPP-4 inhibitor	Vildagliptin	Galvus	23 (7%)
	Sitagliptin	Januvia	12 (4%)

The greater the number of OHA classes prescribed, the faster were the dropout rates, probably due to frequent changes in regimen that led to reduced compliance and

clinic visits. (Figure 5) Similar phenomena were repetitively observed in the study.[3,7,8]

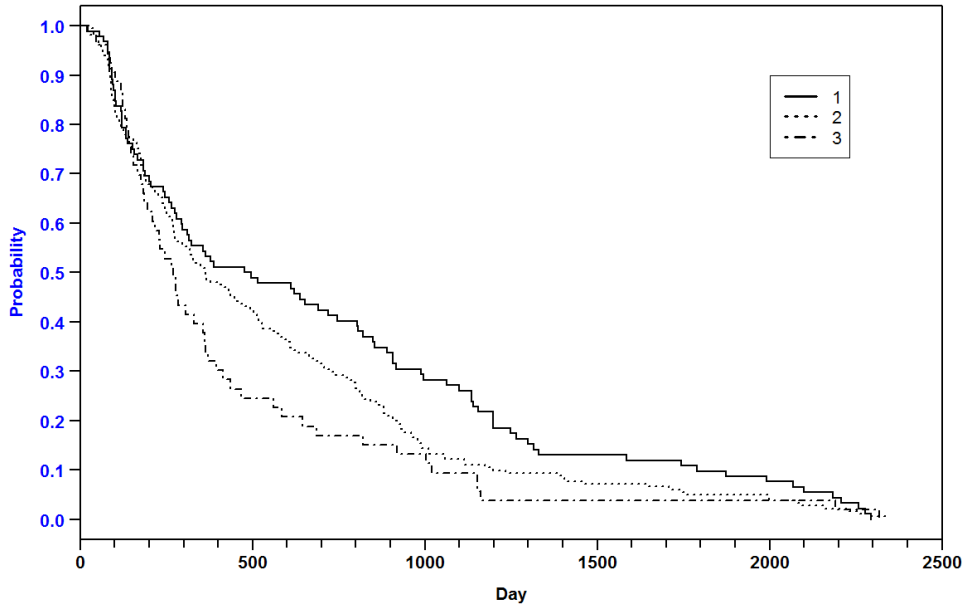

Figure 5. The decreasing rate of patients over time. The number in the legend indicates the number of classes of OHAs prescribed.

The FPG and HbA1c were depicted in Figure 6. The smooth lines for HbA1c and FPG decrease for around 300 days, and then increase after 300 days to 1000 days.

The number of patients without drug prescription was 19 and these patients were excluded from the population analysis because they were not suitable candidates for a placebo effect group. Also, patients whose prescription was changed from the initial prescription were excluded from the analysis. A total of 328 patients were

prescribed 1 to 3 classes of OHAs. The number of OHAs positively correlated with the level of FPG or HbA1c acquired from initial laboratory tests. The decline and rise and the second decline after many dropouts were also observed. (Figure 7)

Figure 6. Fasting plasma glucose (left panel) and glycated hemoglobin (right panels) versus time plots. Dots represent the data (FPG: left panel; HbA1c: right panel) and lines represent smoothing of the data.

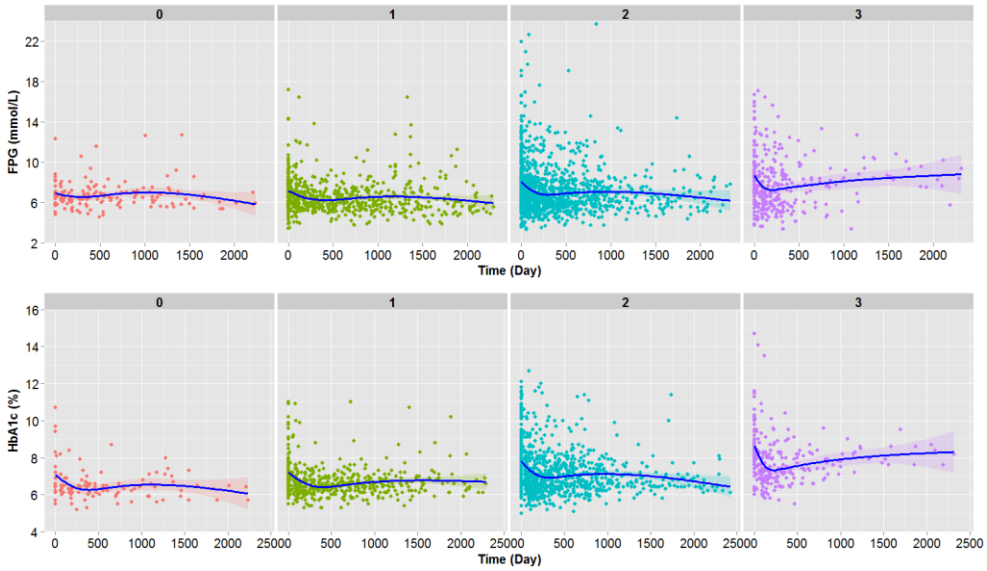

Figure 7. Fasting plasma glucose (upper panels) and glycated hemoglobin (lower panels). Dots and lines represent the data and the smoothing, respectively, and the number indicates the number of classes of OHAs prescribed.

2. Disease Progression Model

The model 3 was selected as the structural model to explain the effects of the OHAs on the baseline and progress rate. Linear models for offset effect and constant model for slope effect were incorporated into the final disease progression model for FPG and HbA1c.

The parameter estimates of the final model for time varying FPG are shown in Table 4. The baseline plasma fasting glucose was 7.94 mmol/L. FPG increased

0.197 mmol/L/year (3.55 mg/dL/year), as part of natural history. The equilibration constant for offset effect was 0.05/day. The half-life for the constant was 13.86 days (=ln2/0.05). Therefore, the maximum offset effect is reached after 55 to 69 days. The rate was significantly slower when α-glucosidase inhibitor was administered. However, it is thought not to have much clinical significance because the number of prescriptions was small and so it could not be representative of this population. Total cholesterol had inverse relationship with the equilibration rate. The amplitude of offset effect (BETA1) increased with the number of prescribed drugs. BETA1 increased depending on the baseline FPG and decreased inversely proportional to diabetes duration. When the duration was 12 years, BETA1 decreased around 26%. Diabetes treatment reduced the slope of disease progression by 6.59%. However, the differences between drugs and number of drugs were not identified. (Table 4, Figure 8)

Table 5 shows the modeling results for HbA1c. The baseline HbA1c was 7.79 mmol/L. The baseline level was inversely proportional to the postprandial C-peptide value. The natural disease progression rate was 0.181%/year and it increased six fold in the case of patients with renal disease, such as chronic renal failure and end stage renal disease. The typical value of equilibration rate constant was 0.0198/day. Therefore, the equilibration half-life was 34.83 day (=ln2/0.0198) and it took around 140 to 175 days to reach pharmacokinetic and pharmacodynamics equilibrium state. The amplitude of offset effect (BETA1) increased with the number of prescribed drugs, though there were little differences between 2 drugs

and 3 drugs. Patients with higher baseline showed higher BETA1 level. Diabetes treatment decreased the slope of disease progression by 10%. However, the differences between drugs and number of drugs were not identified. (Table 5, Figure 8)

The upper panels in Figure 9 show the typical treatment outcome for FPG and HbA1c according to the number of drug classes, predicted by population approach using NONMEM. When the baseline values are equal, the more drugs patients had, the more FPG and HbA1c decreased, indicating that intensive treatment brought better effect. Differences in treatment outcome for FPG clearly appeared to correlate with the number of drugs taken, while those for HbA1c between two drugs and three drugs were not clear. The equilibrium of offset effect for FPG was reached faster than that for HbA1c. Middle and right panels show that conditional weighted residuals had no trends, suggesting adequacy of the model. VPC results are plotted in Figure 10, showing a good overall agreement between the prediction and the data, although several early observations were far above the prediction interval.

Table 4. Parameter estimates of the final model for fasting plasma glucose

Parameter	Covariate model	Θ (RSE%)		ω^2 (CV %) (RSE%)		p-value*
S0 (mmol/L)	$S0= \Theta_{S0} \bullet \exp(\eta_{S0})$	Θ_{S0}	= 7.94 (1.59%)	ω_{S0} %	= 21.4% (9.22%)	
SLOPE (mmol/L/year)	$SLOPE= \Theta_{SLOPE} \bullet \exp(\eta_{SLOPE})$	Θ_{SLOPE}	= 0.197 (38%)	ω_{SLOPE} %	= 166.6% (28.8%)	
KEQ1 (day^{-1})	$KEQ1= \Theta_{KEQ1} \bullet (1 + \Theta_{KEQ1,AGS} \bullet AGS) \bullet$	Θ_{KEQ1}	= 0.05 (17.81%)			
	$(1 + \Theta_{KEQ1,CHOL} \bullet (CHOL-175))$	Θ_{AGS}	= -0.966 (2.23%)			1.00E-05
		Θ_{CHOL}	= 0.011 (0.0011%)			4.40E-04
BETA1	NMED=1: $TVBETA1= \Theta_{BETA11}$	Θ_{BETA11}	= 1.14 (14.8%)			
	NMED=2: $TVBETA1= \Theta_{BETA12}$	Θ_{BETA12}	= 1.29 (9.19%)			
	NMED=3: $TVBETA1= \Theta_{BETA13}$	Θ_{BETA13}	= 1.53 (15.3%)			
	$BETA1= \Theta_{BETA1} \bullet$			ω_{BETA1} %	= 38.5% (48.2%)	
	$(1 + \Theta_{BETA1,BASEFPG} \bullet (BASEFPG-7.11)) \bullet$	$\Theta_{BETA1.BASEFPG}$	= 0.14 (0.00036%)			1.83E-18
	$(1 + \Theta_{BETA1,FIRSTDX} \bullet (FIRSTDX-2)) \bullet$ $\exp(\eta_{BEASE1})$	$\Theta_{BETA1\_FIRSTDX}$	= -0.026 (0.902%)			1.06E-04
BETA2 (mmol/L/year)	$BETA2= \Theta_{BETA2} \bullet \exp(\eta_{BETA2})$	Θ_{BETA2}	= 0.0659 (83%)			
σ^2 (RSE%)		σ_{FPG} %	= 19.9% (1.89%)			

S0, baseline

SLOPE, natural disease progression rate

KEQ1, equilibration constant rate between pharmacokinetics and pharmacodynamics

BETA1, amplitude of the drug effect on offset effect

BETA2, constant slope effect

$\Theta_{Parameters}$: the basic structural fixed-effect parameter;

$\omega_{Parameters}$: the interindividual variabilities for the parameters;

η_{S0}: the interindividual random error for S0 with mean zero and variance ω^2_{S0}

$\sigma_{component}$: the intraindividual variabilities for the fasting plasma glucose

RSE: the relative standard error (= standard error of parameter estimate /parameter estimate)

NMED: number for classes of prescribed drugs

AGS: 0 for no prescription of α-glucosidase inhibitor, 1 for prescription of α-glucosidase inhibitor

CHOL: total cholesterol level at the time of the first treatment

BASEFPG: fasting plasma glucose level at the time of the first treatment

FIRSTDX: diabetes duration

* P-values were obtained by the likelihood ratio test between the models including and excluding a covariate to be tested.

Table 5. Parameter estimates of the final model for glycated hemoglobin

Parameter	Covariate model	Θ (RSE%)		ω² (CV %) (RSE%)		p-value*
S0 (%)	$S0= \Theta_{S0} \cdot (1 + \Theta_{S0,POCP} \cdot POCP) \cdot \exp(\eta_{S0})$	Θ_{S0}	= 7.79 (1.11%)	ω_{S0} %	= 15.1% (9.86%)	
		$\Theta_{S0,POCP}$	= -0.0171 (22.5%)			3.00E-06
SLOPE (%/year)	$SLOPE= \Theta_{SLOPE} \cdot (1 + \Theta_{SLOPE,RNL}.RNL) \cdot \exp(\eta_{SLOPE})$	Θ_{SLOPE}	= 0.181 (26.4%)	ω_{SLOPE} %	= 100% (29.5%)	
		$\Theta_{S0,RNL}$	= 5 (21%)			1.30E-05
KEQ1 (day^{-1})	$KEQ1= \Theta_{KEQ1}$	Θ_{KEQ1}	= 0.0198 (8.87%)			
BETA1	NMED=1: $TVBETA1= \Theta_{BETA11}$	Θ_{BETA11}	= 0.608 (14.8%)			
	NMED=2: $TVBETA1= \Theta_{BETA12}$	Θ_{BETA12}	= 0.693 (9.11%)			
	NMED=3: $TVBETA1= \Theta_{BETA13}$	Θ_{BETA13}	= 0.696 (15.3%)			
	$BETA1= \Theta_{BETA1} \cdot (1 + \Theta_{BETA1,BASEHBA} \cdot (BASEHBA-7.11)) \cdot \exp(\eta_{BETA1}) \cdot$	$\Theta_{BETA1.BASEHBA}$	= 0.14 (0.085873%)	ω_{BETA1} %	= 82.6% (22.1%)	3.85E-01
BETA2 (%/year)	$BETA2= \Theta_{BETA2}$	Θ_{BETA2}	= 0.1023 (36.59%)			
σ^2 (RSE%)		σ_{HBA}%	= 6.68% (2.67%)			

See table 4 for terminology

POCP: values for postprandial C-peptide at the time of the first treatment

RNL: 0 for no renal disease, 1 for renal diseases

BASEHBA: glycated hemoglobin level at the time of the first treatment

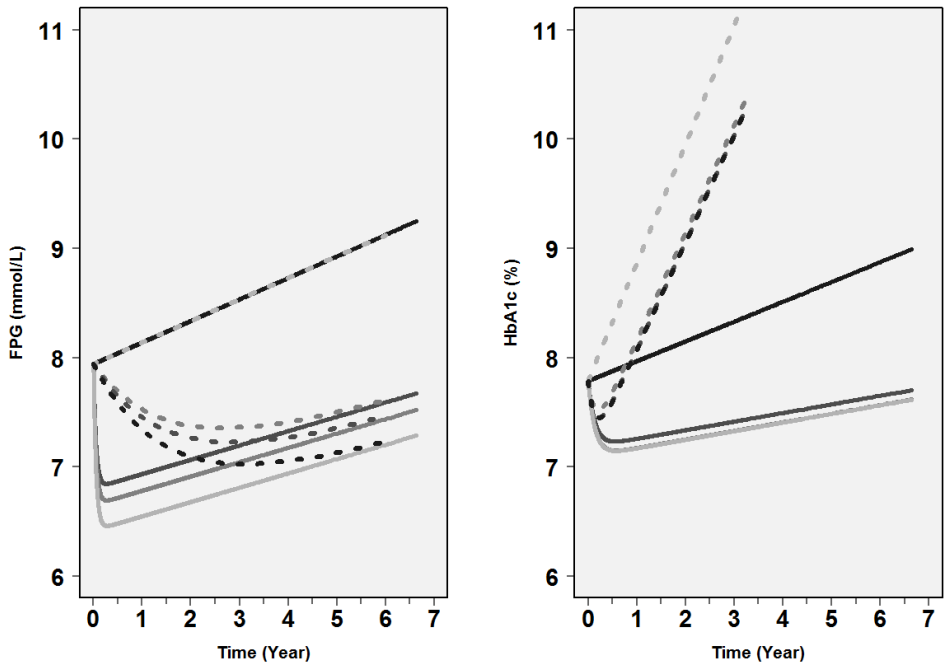

Figure 8. The effect of dichotomous covariates on model. Left panel show the effect of α-Glucosidase inhibitor on FPG model and right panel show the effect of renal disease on HbA1c. Dotted lines represent the existence of the covariates, while the solid lines don't. The four lines represent prediction lines for natural course, one-drug, two- and three-drug groups orderly from the top to the bottom.

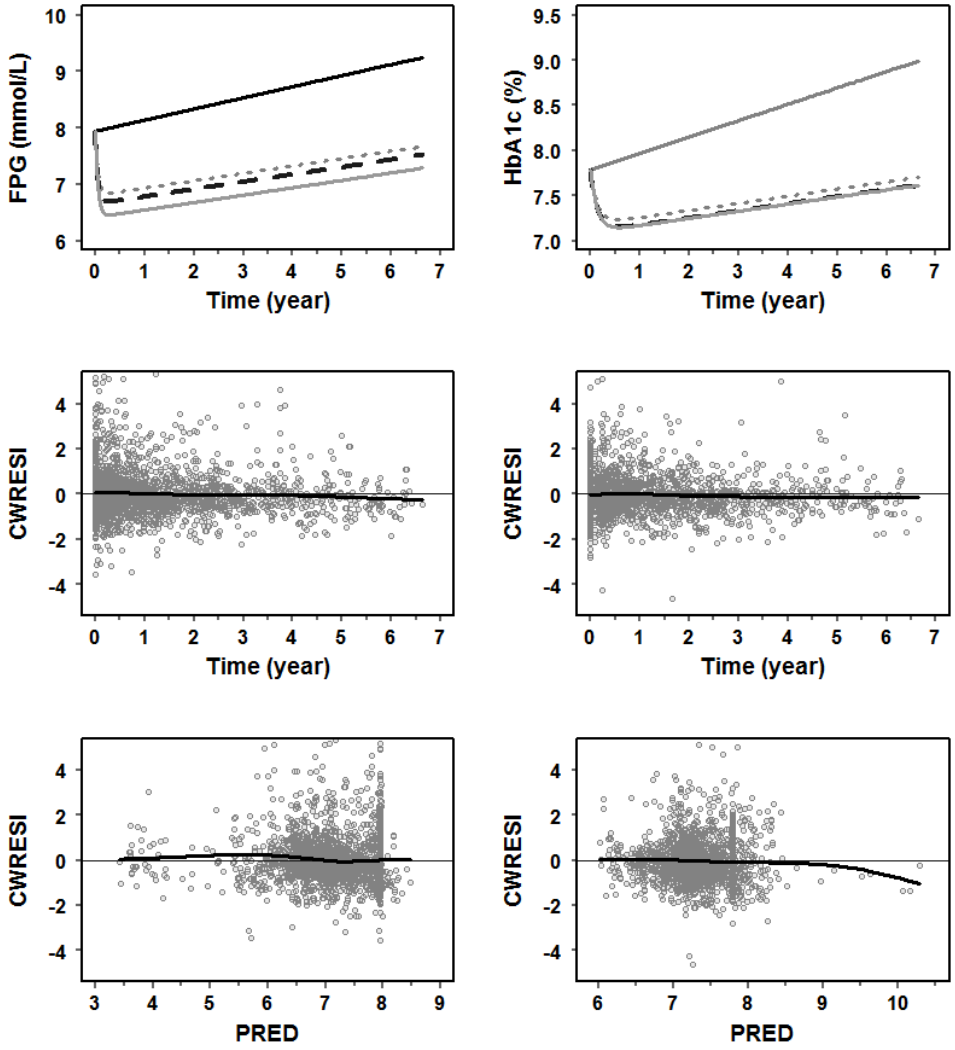

Figure 9. Model Predictions (upper) and goodness of fit plots (mid and lower panels) of the final models. In upper panel, the solid black lines are natural disease course. Dotted gray, dashed black and solid gray lines in left panels are prediction lines for patients who had one drug, two and three drugs, respectively. The dots in mid and lower panels represent conditional weighted residuals. The solid lines in mid and lower panels are smooth lines.

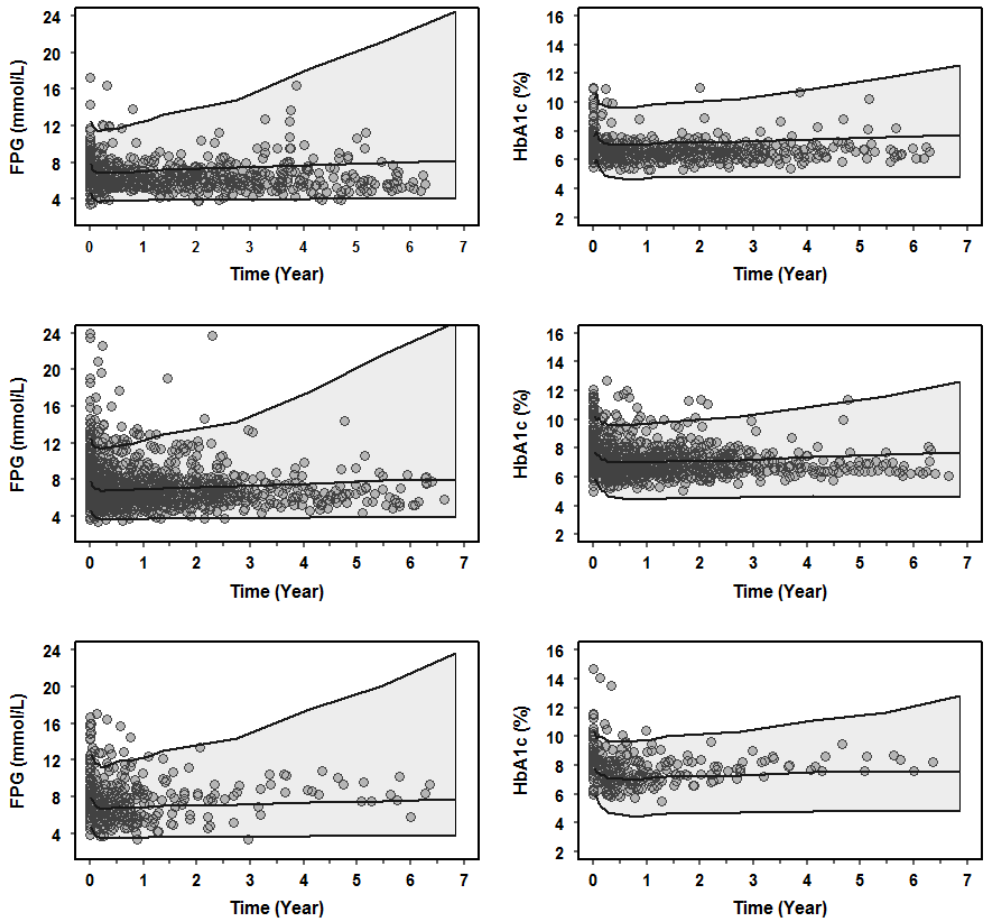

Figure 10. Visual predictive check for the predicted fasting plasma glucose (left) and HbA1c (right) for 1 drug (upper), 2 drugs (middle) and 3 drugs (lower). The gray areas represent the 90% prediction intervals obtained from 1000 datasets simulated from the final model where the thick curve in the middle denotes the 50th percentile.

IV. DISCUSSION

I tried to quantify the pattern of disease progression in Korean patients with type 2 diabetes using population approach. The slope of the natural disease progression, which was assumed to increase linearly, was 0.197 mmol/L/year for FPG and 0.181 %/year for HbA1c. According to ADOPT study in which patients were administered one drug among three drugs around 5 years, the disease progression rates for fasting plasma glucose were 0.039, 0.15 and 0.31 mmol/L/year for rosiglitazone, metformin and glyburide group and those for glycated hemoglobin were 0.07, 0.14 and 0.24, respectively.[4] The more drugs patients were prescribed, the lower the disease status they reached. The effects of covariates on the slope and disease status were reflected. In the case of FPG, total cholesterol, baseline FPG, and disease duration were significantly correlated with the offset effect. The offset effect for HbA1c was proportional to the baseline HbA1c.

Although it is well known that diabetes is a progressive disease and mechanistic or empirical models to explain it has been actively developed,[20,23-26] aspects of long-term disease progression has never been made into a model in Korean population. Furthermore, previous studies cannot be easily applied to routine clinical data in Korea, due to intrinsic limitations. This study has been the first attempt in developing a disease progression model in Korean patients with type 2 diabetes mellitus, using retrospective clinical data obtained from Severance hospital. I could find some covariates which affected progression by analyzing the population parameters and between subject variability.

Frey et al. made a model which explained the effect of gliclazide on lowering the status of the disease using a equilibration constant which could explain the time delay between pharmacokinetics and pharmacodynamics. A study in which FPG, fasting serum insulin and HbA1c of the patients with type 2 diabetes were measured while taking gliclazide, metformin and pioglitazone for a year, had been incorporated into a mechanistic model. I made an empirical model taking a macroscopic view of disease progression and treatment. It could explain the time-varying trend of population disease progression.

There are some limitations in my study. The variability was very high because we retrospectively got this data from real clinical situation, contrary to a well-controlled prospective clinical study. The doses of the drugs were not reflected in this model because there was too small information to build a dose related mode. Another shortcoming was that the characteristics of the six kinds of drugs could not be fully reflected and the effect of each drug was confounding because some drugs were rarely prescribed and more than 1 drug was frequently prescribed to the patients. I plan to overcome this drawback by collecting more data.

V. CONCLUSIONS

This study quantitatively showed the disease progression in Korean patients with type 2 diabetes mellitus using a model-based approach. The estimated disease progression rates of these patients were 0.197 mmol/L/year for FPG and 0.181%/year for HbA1c. The equilibration half-lives of offset effects were 14 days for FPG and 35 days for HbA1c. Treatment effect decreased inversely proportional to diabetes duration. The more drugs patients got, the bigger effect they had. The preliminary results might be helpful for understanding the disease sequelae and managing patients after proper validation processes.

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ABSTRACT (IN KOREAN)

한국인 제2형 당뇨병 환자에서의 질병 진행 모형 개발

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이 동 환

제 2형 당뇨병(type 2 diabetes mellitus)은 진행하는 질병이다. 베타 세포(β-cell)의 기능 감소와 인슐린의 증가는 공복혈당의 증가를 초래한다. 당뇨약물 중에는 질병의 진행 속도를 감소시키거나 질병 상태를 호전 시키는 것들도 있지만 질병의 진행을 멈출 수는 없다. 하지만, 많은 연구를 통해서 집중 치료가 당뇨병으로 인한 심혈관 합병증을 줄일 수 있음이 밝혀졌다. 이것은, 적절한 치료 전략에 의해 당뇨병의 진행이 조절될 수 있다는 것을 방증한다. 계량약리학(pharmacometircs)은 임상약리학

(clinical pharmacology)의 최첨단 분야로서 약물의 작용, 질병의 진행과 환자의 정보를 정량화한 모델을 만들어 효율적인 약물개발과정에 적용될 뿐만 아니라 실제 임상에서도 유용하게 사용될 수 있다. 여기서, 질병 진행 모형은 약물의 작용과 질병의 상태를 정량화 하여 생체지표(biomarker)와 임상결과(clinical outcome)의 관계를 규명하는 역할을 한다. 이 연구의 목적은 한국인 제2형 당뇨병 환자에서의 질병 진행 모형(disease progression model)을 개발하고 나아가 이를 진료에 적용하는 것에 있다.

2006년부터 2012년까지 세브란스병원의 내분비내과를 방문한 초진 환자 888명을 조사하였다. 이 중 1회 방문하거나 검사 결과가 1번밖에 없는 환자 경구투여 당뇨약 이외의 치료를 받은 환자는 제외되고 347명의 자료가 분석에 사용되었다. 1차 평가변수는 공복혈당(fasting plasma glucose)과 당화혈색소(glycated hemoglobin)이었다. 질병 진행 모형은 초기 질병 상태(baseline), 질병의 자연 진행(natural history of progress) 그리고 질병의 상태나 진행 속도에 영향을 주는 약물 효과에 대해서 평가되었다. 약물의 효과는 상수 모형(constant mode), 선형 모형(linear model), 단순 Emax 모형, sigmoid Emax 모형과 power 모형으로 분석되었으며 약동학의 항정상태와 약력학의 항정상태에 도달하는 시간적 차이를 설명하기 위해 효과구획모형(effect compartment model)이 사용되었다. 사용된 약물의 계열과 계열의 숫자가 구조모형(structural model)

의 파라미터에 미치는 영향이 계산되었다. 인구학적 요소도 공변량(covariate)으로서 모형에 주는 영향이 분석되었다. 최종모형은 1000회의 시뮬레이션(visual predictive check)을 통해 평가되었다.

185명의 남자환자와 162명의 여자환자의 나이의 중간값은 61세 (19-85세)이었다. 메트포민(Metformin)이 가장 많이 처방되었고 그 다음으로는 sulfornylurea 계열이었다. 약물을 처방 받지 않은 환자는 19명이었는데 위약효과(placebo effect)를 분석하기에는 그 숫자가 적어 질병진행모형에는 이를 제외한 328명의 자료가 사용되었다. 구조모형에는 약물계열의 수가 질병의 상태에 미치는 효과(offset effect)에 반영되었다. 치료 시작 시점의 공복혈당과 당화혈색소가 높은 경우 많은 약이 처방되는 경향이 있었다. 선형모형과 상수모형이 각각 질병의 상태와 질병의 진행에 영향을 주는 모형으로 선택되었다. 모델링을 통해 나타난 한국인의 당뇨진행속도는 공복혈당의 경우 0.197 mmol/L/year 이었고 당화혈색소의 경우 0.181%/year이었다. 공복혈당의 경우 처방된 약물의 계열 숫자가 많을수록 질병의 상태를 낮추는 효과가 컸고 당화혈색소의 경우 2개와 3개의 차이가 크지 않았다. 약동/약력학 평형상수(equilibration rate constant)의 반감기는 공복혈당의 경우 14일이었고 당화혈색소의 경우 35일로 나타났다. 따라서, 치료 시작 후 반감기의 4~5배인 55일 내지 69일에 공복혈당이 최대로 감소한 이후에는 질병 진행의 기울기에 따라 질병이 진행했으며 당화혈색소의 경우에는 최대효과가 140일 내지 175

일에 나타났다.

본 병원에 내원한 한국인 제2형 당뇨환자의 공복혈당과 당화혈색소의 증가속도(각각0.197 mmol/L/year 와 0.181%/L)는 ADOPT연구에서 밝혀진 공복혈당의 증가속도인 0.039-0.31 mmol/L/year와 당화혈색소의 증가속도인 0.07-0.24 %/L와 유사했다. 치료 시작 후에 공복혈당이 당화혈색소에 비해 빠르게 감소하였다. 치료효과는 유병기간이 길어질수록 감소했다. 처방된 약물 계열의 수가 많을수록 질병의 상태를 낮추는데 효과적이었다. 추가적인 연구를 통해 보다 유용한 질병진행모형을 개발할 수 있을 것으로 생각된다.

핵심되는 말: 제 2 형 당뇨병, 질병진행모형, 공복혈당, 당화혈색소, 정량분석, 집단분석