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Model development for calcium concentration changes after thyroidectomy and calcium supplements effects in Korean population

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Model development for calcium concentration changes after thyroidectomy and calcium supplements effects in Korean population

Directed by Professor Kyungsoo Park

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먼저 5년간 저를 믿어주시고 전폭적인 지지와 깊은 가르침을 주신 지도 교수님, 박경수 교수님께 진심으로 감사 인사를 드리고 싶습니다.

바쁘신 와중에 귀한 시간을 내어 고견을 주신 정웅윤 교수님, 남기현 교수님, 남정모 교수님, 이유미 교수님께도 진심으로 감사를 드립니다. 교수님들의 지도가 아니었다면 이 논문은 나올 수 없었을 것입니다.

약리학교실의 두 기둥이신 김경환 교수님과 안영수 교수님, 약리학교실을 이끌어주시는 김동구 교수님, 이민구 교수님, 김철훈, 김주영, 김형범, 지헌영 교수님께도 감사 드립니다. 교수님들의 헌신이 있기에 약리학교실의 학생들이 믿음을 가지고 연구에 매진할 수 있었습니다.

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ABSTRACT

Model development for calcium concentration changes after thyroidectomy and calcium supplements effects in Korean population

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Hypocalcemia is known as one of the most common complications after thyroidectomy, which can lead to prolonged hospitalization and low quality of life. Although a number of studies have been reported on hypocalcemia so far, no study is found that investigated the longitudinal change of calcium after thyroidectomy. With this background, the objectives of this work are to develop a quantitative model to predict calcium and parathyroid hormone level changes after thyroidectomy in Korean population and to identify associated influencing factors.

The data were collected from clinical data retrieve system (CDRS) and electrical

medical records (EMR) system of Severance Hospital. Included patients were Korean patients aged above 19 when they underwent a thyroidectomy under general anesthesia in Severance Hospital between January and June 2013. Patients who had a past history of thyroidectomy or who underwent thyroidectomy due to secondary hypocalcemia or whose baseline calcium level was missing or who had diseases that can cause hypoalbuminemia were excluded. The analysis variables were plasma calcium and PTH concentrations before and after thyroidectomy and, treatment effect of external calcium supplement, if any, was also analyzed.

Using a non-linear mixed effect modeling approach which is widely used in the analysis of routine clinical data, the model was developed based on the disease progression modeling concept. Basically, turnover model was used to describe changes of endogenous calcium and PTH levels. Feedback effect of calcium on PTH level was included in the model according to the known mechanism of calcium-PTH homeostasis. Not only sudden drops in calcium and PTH levels observed at the early phase immediately after thyroidectomy, but late-phase effects, including the influence of incomplete recoveries from surgery and additional calcium supplements, were considered in developing the model to represent the typical pattern of hypocalcemia observed in patients receiving thyroidectomy. The model was evaluated by goodness of fit plots, Akaike information criterion (AIC) and a visual predictive check (VPC).

The refined model, which is the final model, shows that $Kout_{Ca}$ increases with body weight and radical neck dissection and it decreases with baseline calcium level, $K_{R,Ca}$ decreases with total surgical removal of thyroid, and Amp_p increases with baseline

PTH, total thyroidectomy, number of loss of PTG and old age.

Future works include the external validation of the model to be developed. With a successful validation, it is expected that the model can be used as a supportive tool in efficient management of calcium and PTH levels after thyroidectomy in Korean population.

Key words: Post-thyroidectomy, hypocalcemia, calcium, calcium supplements, NONMEM, disease progression model

Model development for calcium concentration changes after thyroidectomy and calcium supplements effects in Korean population

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I. INTRODUCTION

Thyroidectomy, a surgical removal of thyroid gland, is one of the common surgical procedures in Korea and US.[1,2] Among 1,710,270 surgeries in total conducted in Korea in 2014, thyroidectomy was more than 37,162 cases.[2] Thyroid malignancy was the most frequent reason for thyroid surgery and toxic thyroid disease and clinically significant goiter were also indications for thyroidectomy.[2] While thyroidectomy is an effective treatment for these indications, complications after thyroidectomy such as hypocalcemia and recurrent laryngeal nerve paralysis could affect patient's quality of life.[3,4] These two complications occur due to anatomical structure; the parathyroid glands and recurrent laryngeal nerves are located at the proximity of the thyroid gland.[4]

Hypocalcemia, the most frequent post-thyroidectomy complication, is defined as a total calcium level below 8.0 mg/dl or ionized calcium level below 4.5 mg/dl.[4,5] Symptoms and signs of hypocalcemia include a various range; from mild such as oral numbness, Chvostek's and Trousseau's sign to life-threatening such as laryngospasm and arrhythmia. The known causes of hypocalcemia after surgery are hemodilution during operation, calcitonin release, hungry bone syndrome with hyperthyroidism osteodystrophy and permanent or transient injury of parathyroid gland.[6-9] Because most of these causes are temporary, the decreased calcium levels are spontaneously recovered in 2 - 3 mo, indicating transient hypocalcemia. But some patients' decreased calcium levels persist up to 6 - 12 mo after thyroidectomy, indicating permanent hypocalcemia.[5] In addition to lowering quality of life, post-thyroidectomy hypocalcemia is the major factor for prolonged hospitalization and it could increase medical cost directly or indirectly.[5,7] So, there have been a lot of efforts to prevent hypocalcemia after surgery. Not only improved operational skills, like autotransplantation of removed parathyroid gland, but also prophylactic calcium and vitamin D supplements have been suggested to decrease the incidence of hypocalcemia.[10-12] But others suggest that routine calcium supplementation is controversial and selective calcium supplementation to high risk patients is safer and more effective than routine prophylaxis.[13]

To select patients who need to receive calcium supplementation, identification of predictors for hypocalcemia after thyroidectomy would be essential. A number of studies to find accurate predictors for hypocalcemia and/or hypoparathyroidism have

been conducted.[5-9,13-19] Among them, some predictors, including the number of identified parathyroid gland, showed the consistent result between studies but others did not.[18] However, these previous studies investigated the cross-sectional nature of hypocalcemia and hypoparathyroidism, only focusing on the specific time point after thyroidectomy, neglecting changes in calcium and PTH levels over the course of time. So there is no information available on time courses and cause-and-effect relationships and physiological interpretations.

Because calcium plays a critical role in human physiology, plasma calcium concentration is controlled within a narrow range by calcium homeostasis, a complex process of many organs and hormones,[20,21] which could be affected by various factors over a long period of time. However, studies reported so far focused on acute changes in calcium level over a short period of time as early as few hours[22,23] or 24 hr after dosing of calcium or recombinant human PTH.[24] One paper is on modeling of calcium and PTH levels after calcium intake in healthy Korean volunteers.[25] But it was a controlled data analysis over 8 hr period. Thus, until now there has been no work reported on quantitative analysis of hypocalcemia in Korean clinical population including those who received thyroidectomy.

For these reasons, the objectives of this study are to develop a quantitative model to predict calcium and parathyroid hormone level changes after thyroidectomy in Korean population and to identify associated influencing factors to help management of post-thyroidectomy hypocalcemia.

II. MATERIALS AND METHODS

1. Data

The data were collected from clinical data retrieve system (CDRS) and electrical medical records (EMR) system of Severance Hospital. Included patients were Korean patients aged above 19 when they underwent a thyroidectomy under general anesthesia in Severance Hospital between January and June 2013. The data was collected up to July 2014 to obtain the enough information to decide if hypocalcemia would be persistent and irreversible. Plasma calcium and PTH concentrations before and after thyroidectomy and dosing information on calcium supplement, if any, were obtained sequentially.

Potential covariates which were expected to be related to calcium level changes were also collected; age, gender, body weight, vitamin D, serum phosphate, alkaline phosphatase (ALP), albumin levels, the characteristics of pathologic lesion, type of thyroidectomy, node dissection and parathyroid gland loss. Potential covariates were first selected based on calcium physiology and previous studies. Among them, some factors which were highly homogenous (> 95%), such as histology, autotransplantations of removed parathyroid gland and past history of thyroid diseases, and which were difficult to be obtained, such as surgeon volumes, were excluded.

Patients who had a past history of thyroidectomy or who underwent thyroidectomy due to secondary hypocalcemia or whose baseline calcium level was missing or who had diseases that can cause hypoalbuminemia were excluded. Additionally, patients

who had no baseline calcium or PTH records were excluded.

2. Model development

This study aimed to develop a model for calcium and PTH level changes after thyroidectomy using retrospectively collected clinical data. To analyze routine clinical data quantitatively, Non-linear Mixed effect modeling method was used.[26] Non-linear mixed effect modeling method is a widely used approach which has advantages to analyze sparse and unbalanced routine clinical data and covariates analysis to identify influencing factors.[27-29]

The inter-individual variability (IIV) was described by exponential model and was neglected if it was too small to estimate.

$$Pij = TVPj * exp^{\eta_{ij}} \quad (1)$$

Where Pij is the jth parameter estimate for the individual i, $TVPj$ is the typical parameter value of the jth parameter and η_{ij} is the individual-specific inter-individual random variable for individual i which followed a normal distribution $N(0,\omega_j^2)$.

The residual variability was tested in three ways; (1) additive, (2) proportional and (3) combined model.

$$C_{ij} = \widehat{C_{ij}} + \varepsilon_{aij} \quad (2)$$

$$C_{ij} = \widehat{C_{ij}} * (1 + \varepsilon_{pij}) \quad (3)$$

$$C_{ij} = \widehat{C_{ij}} * (1 + \varepsilon_{pij}) + \varepsilon_{aij} \quad (4)$$

Where C_{ij} is the *j*th measured observation in *i*th individual, $\widehat{C_{ij}}$ is the *j*th model prediction in *i*th individual and ε_{aij} and ε_{pij} are the additive and proportional residual errors for the *j*th measured observation in *i*th individual which followed a normal distribution $N(0,\sigma_a^2)$ for additive residual error and $N(0,\sigma_p^2)$ for proportional residual error.

A. Model for disease progression of calcium and PTH level change after thyroidectomy

Disease progression refers to natural course of disease status changes.[30-32] In this paper, disease status refers to calcium and PTH levels at a particular time point. Calcium and PTH are endogenous substances. If the patients did not have any other physiological disorder, except for thyroidectomy, the calcium and PTH concentrations would be expected to be recovered to the baseline level measured before thyroidectomy. Turnover model, parameterized with production and elimination rate constants, is generally used to describe homeostasis of endogenous compounds[33] and

previous studies used turnover model as a base to depict calcium and PTH levels.[22,25] Usually, the production process is depicted by a zero-order kinetics and the loss process is depicted by a first-order kinetics. At equilibrium, the production rate is identical to loss rate, with no net change in the system.[33]

PTH is a key factor of the calcium concentration regulation in calcium homeostasis processes.[20,21] PTH is known to be responsible for increasing calcium concentration via activating bone resorption, calcium reabsorption in kidney and intestinal calcium intake using vitamin D.[20,21] Taking this into account, PTH's positive feedback effect, which was not considered in previous studies due to a short observation period,[22,25] was evaluated in this study by assuming that feedback increases the production of calcium concentration

And also, PTH level is regulated by calcium concentration through negative feedback. When extracellular calcium level increases and the number of occupied calcium-receptor complex increases, calcium sensing receptor (CaSR) would be activated and PTH secretion would be inhibited.[22,34,35] Negative feedback via CaSR was implemented assuming that it acts on the process of PTH formation, similar with the Abraham *et al.*'s work.[22]

In this study, all subjects underwent some kind of thyroidectomy. As mentioned above, after thyroidectomy the calcium and PTH levels could be decreased via reversible causes; hemodilution, transient calcitonin release, recoverable injury and/or devascularization of parathyroid gland.[6-9] Because all these causes interact with each

other, they cannot be easily distinguished. So, these recoverable effects of thyroidectomy were lumped together, denoted as E_{OP}.

The differential equations for the model were written as:

$$\frac{\mathrm{d}Ca}{\mathrm{dt}} = Kin_{Ca} * E_{OP_{Ca}} * E_{feed\_PTH} - Kout_{Ca} * Ca \quad (5)$$

$$\frac{\mathrm{d}PTH}{\mathrm{dt}} = Kin_{PTH} * E_{OP_{PTH}} * E_{feed\_Ca} - Kout_{PTH} * PTH \quad (6)$$

Where Ca and PTH are calcium and PTH concentrations, Kin_{Ca} and Kin_{PTH} are the turnover rate of calcium and PTH concentrations, $Kout_{Ca}$ and $Kout_{PTH}$ are the fractional turnover rate of calcium and PTH concentrations, $E_{OP_{Ca}}$ and $E_{OP_{PTH}}$ are the recoverable effect of the thyroidectomy for calcium and PTH levels, E_{feed_PTH} and E_{feed_Ca} are the feedback effect via PTH and calcium levels in the plasma.

At the initial state prior to thyroidectomy, assuming no net change in calcium and PTH levels, it becomes $\frac{\mathrm{d}Ca}{\mathrm{dt}} = 0$ and $\frac{\mathrm{d}PTH}{\mathrm{dt}} = 0$. Then, from Eq. (5) and (6), we can get Ca(0) = $\frac{Kin_{Ca}}{Kout_{Ca}}$ and PTH(0) = $\frac{Kin_{PTH}}{Kout_{PTH}}$ with Ca(0) and PTH(0) being calcium and PTH concentrations at the baseline, respectively.

There were some patients whose calcium and/or PTH levels kept decreasing until 6 - 12 mo after surgery. These incomplete recoveries were also included in the analysis to identify influencing factors to persistent hypocalcemia.

B. Model for calcium supplement effect on disease progression of calcium and PTH levels

In the aspect of disease progression model, drug effect refers to the effect of a drug on disease status.[30-32] In this paper, the drug effect refers to the effect of extra calcium supply, except dietary supplements of calcium. The extra calcium supply was not given to all patients but it might have been given to patients who suffered from low level of calcium. So, it might be possible to separate the drug effect from the natural course. Because the Ca meant the calcium concentration, the amount of calcium externally given should be converted to concentration dimension via a scale parameter, V. Once the external calcium entered the plasma, it is distributed and eliminated according to the same kinetics as given in Equation (5).

So, the differential equation for the overall calcium concentration was modified as:

$$\frac{\mathrm{d}Ca}{\mathrm{dt}} = Kin_{Ca} * E_{OP_{Ca}} * E_{feed_{PTH}} - Kout_{Ca} * Ca + E_{drug}/V \qquad (7)$$

Here, E_{drug} is the amount of external calcium supplements given per day.

The basic model structure is shown in **Figure 1**.

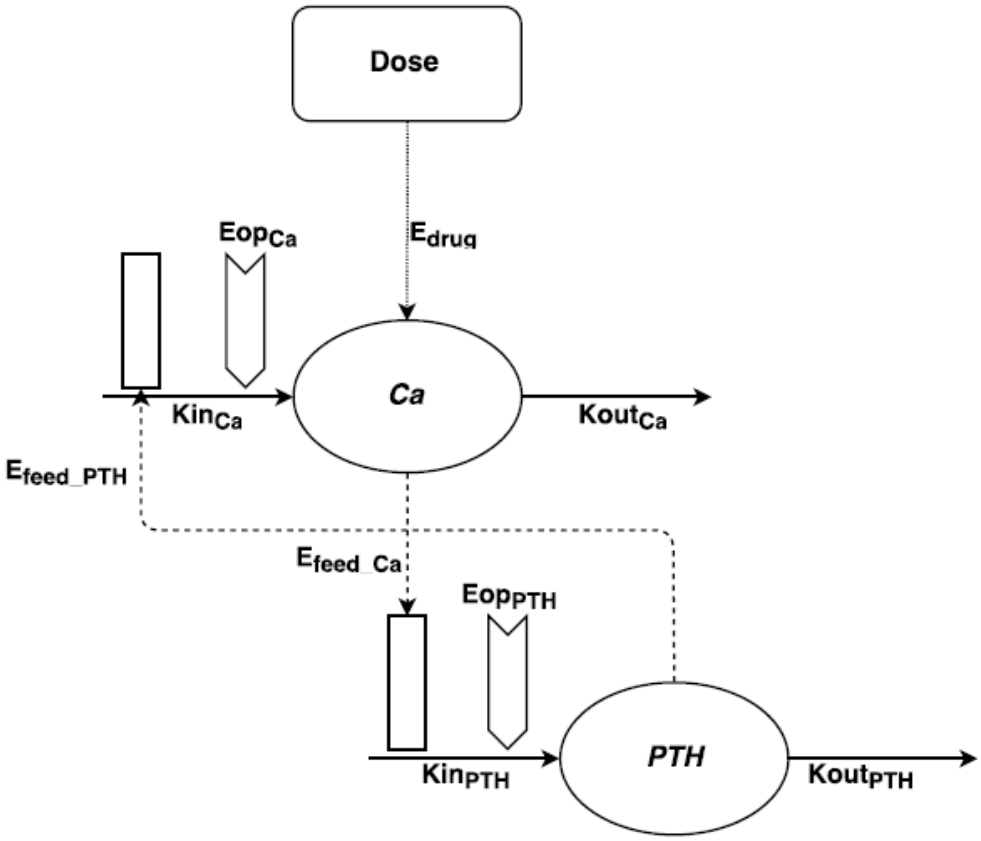


Figure 1. Schematics of the basic model. Kin_{Ca} : the turnover rate of calcium level, Kin_{PTH} : the turnover rate of PTH level, $Kout_{\_\mathrm{Ca}}$:the fractional turnover rate of calcium level, $Kout_{\_\mathrm{PTH}}$: the fractional turnover rate of PTH level, E_{OP_Ca} : the recoverable effect of the thyroidectomy on calcium level, E_{OP_PTH} : the recoverable effect of the thyroidectomy on PTH level, E_{feed_Ca} : the feedback effect from calcium level (via CaSR), E_{feed_PTH} : the feedback effect from PTH level, E_{drug}: the effect of the exogenous calcium supplements on calcium level.

C. Covariate model building

After a base model was selected, to identify the influencing factors associated with hypocalcemia, a stepwise covariate model building approach was performed.[36] Potential covariates selected based on calcium physiology and previous studies on risk factors were tested whether they would improve the model significantly or not. First, starting from the base model, all potential covariates were tested one at a time and the most significant one was retained according to statistical criteria. In next step, the same forward inclusion procedure was performed from the latest model until there was no more covariate left satisfying the criteria. After a full mode is obtained, the backward deletion procedure was performed where the included covariates were deleted from the full model one at a time.

The statistical significance was set to $\alpha = 0.05$ during forward inclusion step and $\alpha = 0.01$ during backward deletion step. The criteria of the statistical test were based on the χ^2-distribution because the difference in objective function value (OFV) of NONMEM between full and reduced models assumed in covariate model building is approximately χ^2-distributed.[37]

Then, model refinement was performed by deletion of imprecisely estimated covariate coefficients to improve the precision of other parameter estimates. The impreciseness was defined as % relative standard error (%RSE) of a coefficient larger than 50%.

3. Model Evaluation

The model was evaluated by goodness of fit plots, the difference of OFV between full and nested models,[37] Akaike information criterion (AIC).[38] With the final model, it was additionally evaluated using a bootstrap[39] and a visual predictive check (VPC).[40] The bootstrap is a method to evaluate the reliability and stability of the parameter estimates with a repeated random sampling from the original data. In this study, 100 random replicates were used. Using the results from the bootstrap sample, nonparametric confidence intervals of parameter estimates were obtained. The VPC is a diagnostic method to compare the distributions of observed and simulated data. In this study, 1,000 simulated datasets were generated and the 10th, 50th and 90th percentiles of observed and simulated data at each time bin were plotted.

4. Analysis Software

Non-linear mixed effect modeling was conducted using NONMEM version 7.3 (ICON Development Solutions, Hanover, MD, USA).[41] First order conditional estimation with interaction (FOCEI) method was used for the analysis. To perform the covariate model building and the model evaluation step as mentioned above, Perl-speaks-NONMEM (PsN) version 4.2 was used for stepwise covariate modeling (SCM), bootstraps and visual predictive check (VPC).[42,43] Goodness of fit and visual

predictive check (VPC) plots were conducted using R version 2.15.0 and Xpose[44] version 4.3.5. An application software to perform model predictions for calcium and PTH level change was developed using R version 3.3.2 and Shiny package.[45]

III. RESULTS

1. Data

From total 1142 patients, 5575 plasma calcium concentrations and 5630 PTH concentrations were collected. Among them, 596 patients had at least one record of dosing history. The patients' characteristics are shown in **Table 1**.

Table 1. Patients' characteristics

Continuous characteristics	**Median (IQR)**
Age (yrs)	43 (35 – 53)
Weight (kg)	60 (54 – 68)
; missing in 59 patients	
Baseline calcium concentration (mg/dl)	9.1 (8.9 – 9.4)
Baseline PTH concentration (pg/ml)	45.40 (36.12 – 57.80)
Baseline inorganic phosphate (mg/dL)	3.6 (3.3 – 4.0)
; missing in 5 patients	
Baseline albumin (g/dL)	4.4 (4.2 – 4.6)
; missing in 5 patients	
Baseline ALP (IU/L)	48 (40 – 59)
; missing in 7 patients	
Baseline 25-OH-vitamin D (ng/mL)	12.24 (8.71 – 16.97)

; missing in 457 patients

Categorical characteristics	Category	Number (%)
Sex	Male	220 (19%)
	Female	922 (81%)
Types of thyroidectomy	Total thyroidectomy	553 (48%)
	Subtotal thyroidectomy	151 (13%)
	Hemithyroidectomy or lobectomy	438 (38%)
Methods of thyroidectomy	Open	821 (72%)
	Robot	301 (26%)
	Endoscopic and/or Minimally invasive	20 (2%)
Neck dissection*	None	36 (3%)
	CCND	1011 (89%)
	MRND	89 (8%)
	Regional	6 (1%)
Histology	Benign	79 (7%)
	Papillary	1047 (92%)
	Follicular	12 (1%)
	Hurthle cell	1 (<1%)
	Poorly differentiated	1 (<1%)
	Anaplastic	2 (<1%)

T-stage	Benign	79 (7%)
	T1	532 (47%)
	T2	4 (<1%)
	T3	512 (45%)
	T4	15 (1%)
Lymph node metastasis	Benign	79 (7%)
; Insufficient specimen 7 (< 1%)	Negative	670 (59%)
	positive	386 (34%)
Parathyroid gland loss	0	753 (66%)
	1	347 (30%)
	2	41 (4%)
	3	1 (<1%)
Parathyroid autotransplantation	Yes	16 (1%)
	No	1126 (99%)

IQR: Inter Quartile Range, *CCND: Central compartment neck dissection, MRND: Modified Radical Neck Dissection

2. Model development

A. Model for disease progression of calcium and PTH level change after thyroidectomy

Basically, turnover model was used to describe changes of endogenous calcium and

PTH levels. At first, the process of the formation of PTH was described with a virtual precursor model, similar with Abraham *et al.*'s work.[22] However the model was unstable and needed huge computing time, more than several weeks. Hence, PTH formation was simplified as a zero-order process.

The negative feedback on PTH level by Ca was applied via CaSR as proposed in *Abraham et al.*'s work. [22] E_{feed_Ca} in Equation (6) was described as:

$$E_{feed\_Ca} = 1 + \rho' * m \tag{8}$$

$$\rho' = \frac{\rho(0) - \rho}{\rho(0)} \tag{9}$$

$$\rho = \frac{Ca^{2+}}{K_D + Ca^{2+}} \tag{10}$$

Where $\rho(0)$ is the baseline CaSR occupancy, m is the slope parameter of the negative feedback effect via CaSR and K_D is the dissociation constant of calcium ion with CaSR. The value of K_D was fixed to 5 mg/dl based on the previous model (*Abraham et al. 2009).*[22] In Eq. (10), to convert the scale from calcium to calcium ion, 0.45 was multiplied to observed total calcium concentration. Similarly to previous work, the slope m was fixed to a value obtained from initial run due to its instability. In our model, the m was not related to the baseline PTH level ($PTH(0)$).

E_{feed_PTH}, the effect of feedback from PTH on calcium turnover, was described as:

$$E_{feed\_PTH} = 1 + (\frac{PTH - PTH(0)}{PTH(0)}) * l \quad (11)$$

Where l is the slope parameter for PTH feedback on Ca change.

Unlike E_{feed_Ca}, E_{feed_PTH} was modeled via an empirical function instead of a mechanistic model.[33] This is because PTH feedback is known to result from several different mechanisms; stimulated bone resorption, decreased renal clearance of calcium and vitamin D activation promoting the gastrointestinal absorption of calcium.[20]

Several functions for the recoverable effects of thyroidectomy, E_{OP}, were tested; (12) monoexponential, (13) Bateman and (14) modified Bateman function.

$$E_{OP} = 1 - e^{-K_R * t} \quad (12)$$

$$E_{OP} = 1 - (e^{-K_{R1} * t} - e^{-K_{R2} * t}) \quad (13)$$

$$E_{OP} = 1 - t * e^{-K_R * t} \quad (14)$$

Where K_R is a rate constant for the decay of the reversible thyroidectomy effect and t is the time. When t is zero, the baseline status would follow homeostasis and $E_{OP}(0) = 1$. Among them, the monoexponential function (Equation (12)) was best.

Incomplete recovery was described as:

$$\widehat{Ca} = Ca - Amp\_c * (1 - e^{-Kout_{Ca}*t}) \quad (15)$$

$$\widehat{PTH} = PTH - Amp\_p * (1 - e^{-Kout_{PTH}*t}) \quad (16)$$

Where $\widehat{Ca}$ and $\widehat{PTH}$ represent the individual predictions of the calcium and PTH concentration, Amp_c and Amp_p represent the amplitudes of the incomplete recovery of calcium and PTH concentration after enough time. The rate constants were assumed as $Kout$, fractional turnover rate of calcium and PTH to reduce the number of parameters and the model complexity.

B. Model for calcium supplement effect on disease progression of calcium and PTH levels

Extra calcium was supplied either by oral administration, intravenous injection or by intravenous infusion. For the oral dose, however, the absorption rate constant was unable to be estimated because observation intervals are in days which were too wide to discern absorption phase from the data. So, the oral administration was treated as intravenous injection. In this model, E_{drug} in the Equation (7) was described as:

$$E_{drug} = \frac{Daily\ Dose}{1\ day} \text{ (unit : mg/day)} \quad (17)$$

Then, using Equations (8), (9), (11), (12) and (17), Equations (5) and (6) were rewritten as:

$$\frac{\mathrm{d}Ca}{\mathrm{dt}} = Kin_{Ca} * \left(1 - e^{-K_{R\_Ca} * t}\right) * \left(1 + \frac{PTH - PTH(0)}{PTH(0)} * l\right) - Kout_{Ca} * Ca + \frac{Daily\ Dose}{1\ day} / V \quad (18)$$

$$\frac{\mathrm{d}PTH}{\mathrm{dt}} = Kin_{PTH} * \left(1 - e^{-K_{R\_PTH} * t}\right) * \left(1 + \frac{\rho(0) - \rho}{\rho(0)} * m\right) - Kout_{PTH} * PTH \quad (19)$$

After integrating the differential equations Equation (18) and (19), incomplete recovery of the late-phase of calcium and PTH levels were applied as Equation (15) and (16).

The estimates of the basic model parameters are shown in **Table 2**. Proportional models were selected as the residual error model of calcium and PTH level. The inter-individual variability of Amp_c was over 100% and that of $K_{R,Ca}$ was almost 80%. Except the inter-individual variability of V, all relative standard error (RSE (%)) of parameters were lower than 25%, indicating the precision of estimated parameters were acceptable.

Table 2. Estimates of the basic model parameter

Model parameters (unit)	Parameter estimates (%RSE)	Shrinkage, %
Structural model		
Ca(0) (mg/dL)	9.17 (0.181)	
PTH(0) (pg/mL)	47.0 (1.63)	
$Kout_{Ca}$ (/day)	0.125 (3.15)	
$Kout_{PTH}$ (/day)	0.930 (3.36)	
$K_{R,Ca}$ (/day)	1.31 (12.1)	
$K_{R,PTH}$ (/day)	0.763 (10.5)	
V (L)	2340 (52.6)	
m	0.0398 fixed	
l	0.444 (23.2)	
Amp_c (mg/dL)	0.204 (20.1)	
Amp_p (pg/mL)	11.8 (7.81)	
Inter-individual Variability		
ω (*Ca(0)*) (%CV)	1.93 (13.8)	49.044
ω (*PTH(0)*) (%CV)	22.5 (5.17)	21.052
ω ($Kout_{Ca}$) (%CV)	20.4 (15.4)	62.153
ω ($K_{R,Ca}$) (%CV)	79.6 (8.91)	34.773
ω (Amp_c) (%CV)	116 (9.07)	53.834
ω (Amp_p) (%CV)	48.8 (10.0)	38.762

Residual Variability		
$\sigma_{proportional\_Ca}$ (%CV)	4.62 (2.79)	11.419
$\sigma_{proportional\_PTH}$ (%CV)	32.4 (2.00)	7.9812

C. Covariate selection

In the covariate selection step, potential covariates were first selected based on calcium physiology and previous studies. The selected covariates were preliminarily examined by univariate analysis and graphical representations for the relationship between covariates and post-hoc individual parameter estimates obtained from the basic model. Then, the covariates were formally tested using the stepwise covariate model building whether they would improve the model significantly as compared to basic model. In doing so, despite a strong correlation with the type of thyroidectomy ($p<0.0001$, not shown), *Amp_c* was not tested due to possible confounding effects with vitamin D supplements externally given to recover decreased calcium levels.

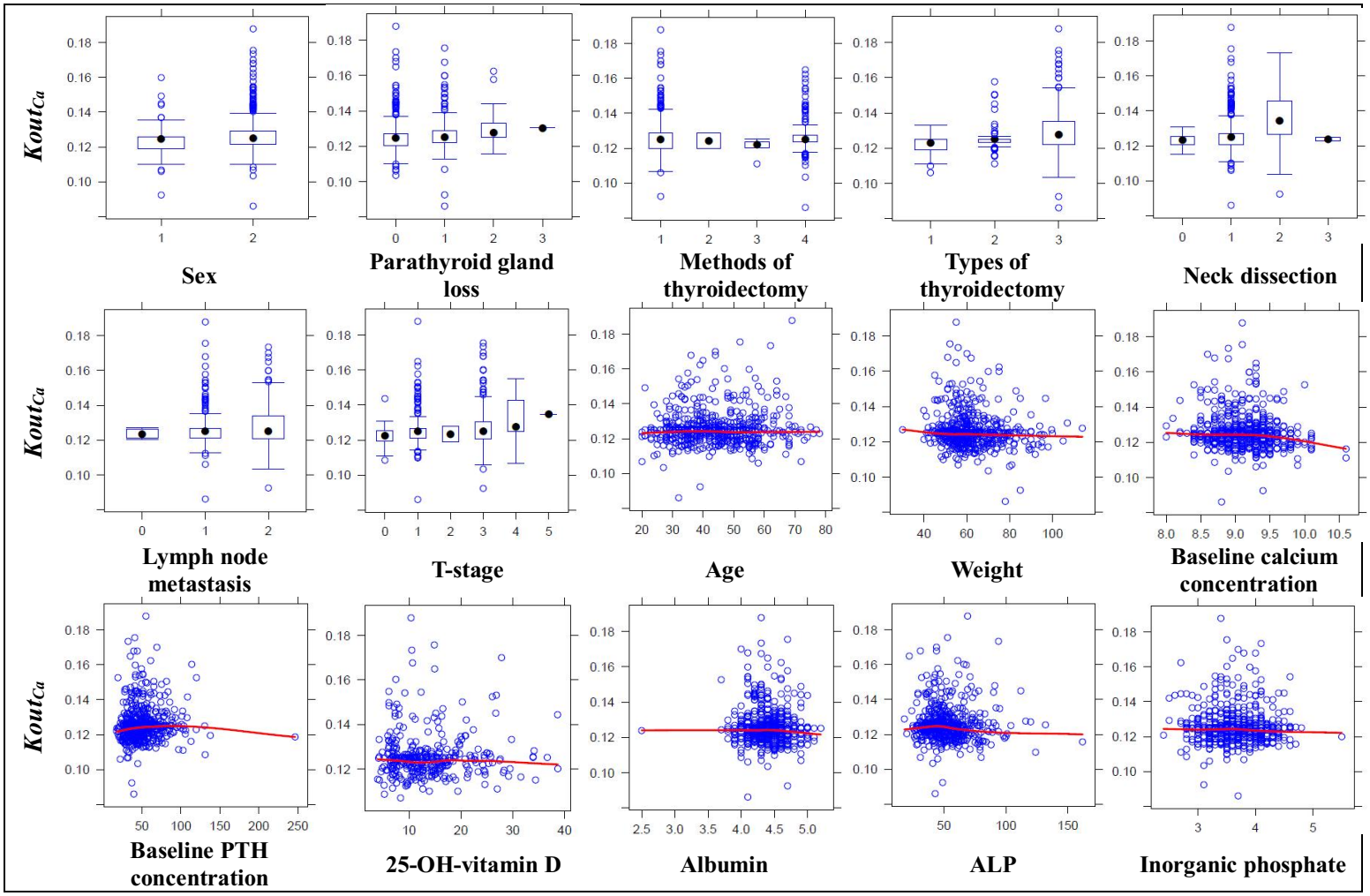
Preliminary examination results for covariate-parameter relationships are reported in **Table 3** for univariate analysis and **Figure 5** for graphical representations. Among the potential influencing factors, the type of thyroidectomy was the most significant factor on $Kout_{Ca}$, $K_{R,Ca}$, and *Amp_p* ($p < 10^{-30}$). The level of neck dissection was also highly related to $Kout_{Ca}$, $K_{R,Ca}$, and *Amp_p* ($p < 0.001$) (**Table 3**).

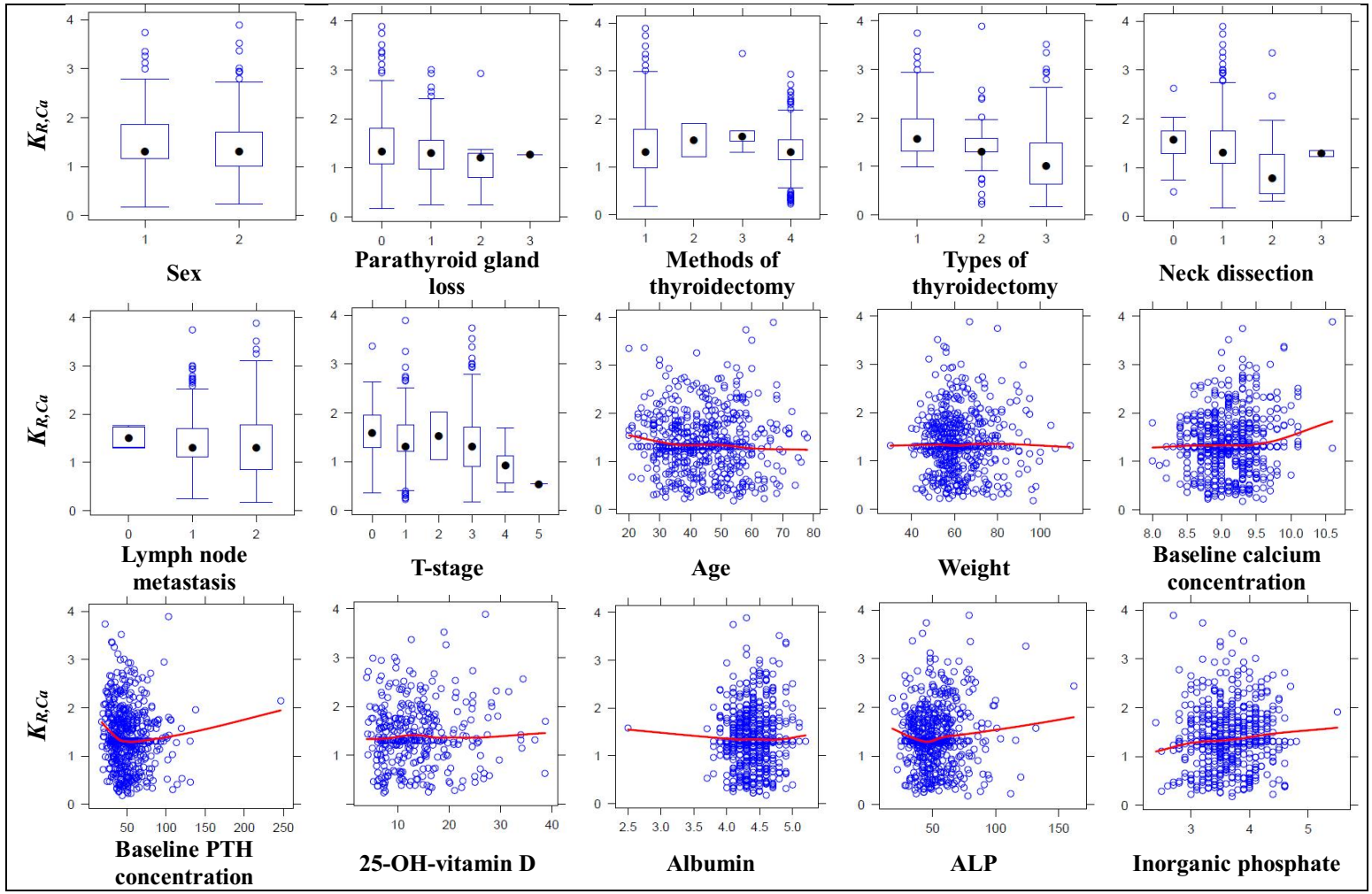
Table 3. The significance of each covariate-parameter relationship

	$Kout_{Ca}$	$K_{R,Ca}$	*Amp_p*
Age	0.40	0.11	0.00024^{***}

Weight	0.24	0.045*	0.49
Baseline calcium concentration	0.000039****	0.026*	0.19
Baseline PTH concentration	0.14	0.18	0.000001****
Inorganic phosphate	0.99	0.73	0.43
Albumin	0.97	0.82	0.43
ALP	0.43	0.72	0.99
25-OH-vitamin D	0.56	0.46	0.95
Sex	0.0017**	0.39	0.089
Types of thyroidectomy	$2.99*10^{-31}$****	$5.38*10^{-35}$****	$3.88*10^{-34}$****
Methods of thyroidectomy	0.089	0.10	0.12
Neck dissection	0.000077****	0.00029***	0.000014****
T-stage	0.027*	0.014*	0.014*
Lymph node metastasis	0.0029**	0.071	0.00021***
Parathyroid gland loss	0.019*	0.0059**	0.00096***

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$





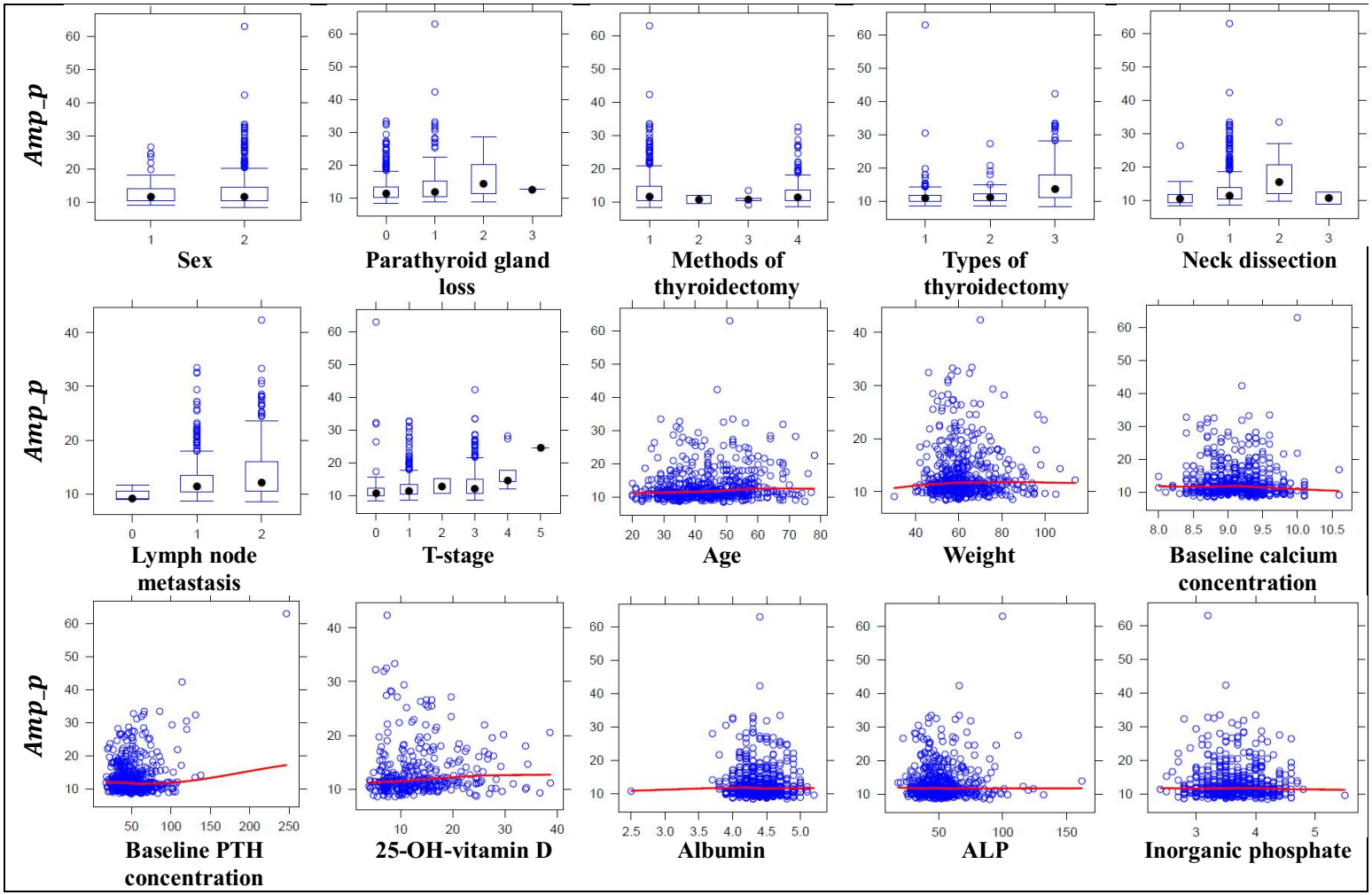


Figure 2. **Graphical representations of the covariate-parameter relationships.** Solid red lines represent smoother lines. Sex: 1 for male and 2 for female; Parathyroid gland loss: 0, 1, 2, 3 for the number of parathyroid gland loss; Methods of thyroidectomy: 1 for open surgery, 2 for minimal invasive surgery, 3 for endoscopic surgery and 4 for robot surgery; Types of thyroidectomy: 1 for hemithyroidectomy or lobectomy, 2 for subtotal or near total thyroidectomy and 3 for total thyroidectomy; Neck dissection: 0 for none, 1 for CCND, 2 for MRND and 3 for regional neck dissection; Lymph node metastasis: 0 for benign, 1 for negative and 2 for positive; T-stage: 0 for benign, 1 ,2,3 for T1, T2, T3 and 4,5 for T4a and T4b.

Then, the stepwise covariate model building results are represented in **Table 4** and **Table 5**. The covariates selected to be significant after the stepwise covariate model building were baseline PTH and type of thyroidectomy for $K_{R,Ca,}$ body weight, neck dissection and baseline calcium level for $Kout_{Ca}$ and baseline PTH, loss of parathyroid glands, type of thyroidectomy and age for *Amp_p.*

Table 4. Covariates added at each step (Forward selection)

	Covariate	OFV_{OLD}	OFV_{NEW}	ΔOFV	Criterion	d.f.	P-value
Step 1	Type of thyroidectomy on $K_{R,Ca}$ *(linear)*	15967.38	15809.56	157.82	5.99	2	5.38×10^{-35}
Step 2	Type of thyroidectomy on *Amp_p* *(linear)*	15809.56	15654.06	155.50	5.99	2	1.71×10^{-34}
Step 3	Baseline PTH on *Amp_p* *(linear)*	15654.06	15635.66	18.40	3.84	1	0.000018
Step 4	Baseline calcium on $Kout_{Ca}$ *(linear)*	15635.66	15617.55	18.11	3.84	1	0.000021
Step 5	Parathyroid gland loss on *Amp_p* *(linear)*	15617.55	15599.94	17.61	7.81	3	0.00053
Step 6	Age on *Amp_p* *(linear)*	15599.94	15590.13	9.81	3.84	1	0.0017
Step 7	Weight on $Kout_{Ca}$	15590.13	15582.31	7.82	3.84	1	0.0052

	(linear)						
Step 8	Node dissection on $Kout_{Ca}$ *(linear)*	15582.31	15569.04	13.27	7.81	3	0.0041
Step 9	Weight on $Kout_{Ca}$ *(piece-wise linear)*	15569.04	15564.62	4.42	3.84	1	0.035
Step 10	Weight on $K_{R,Ca}$ *(linear)*	15564.62	15559.74	4.88	3.84	1	0.027
Step 11	Baseline PTH on $K_{R,Ca}$ *(linear)*	15559.74	15555.20	4.54	3.84	1	0.033
Step 12	Baseline PTH on $K_{R,Ca}$ *(piece-wise linear)*	15555.20	15546.92	8.27	3.84	1	0.0040
Step 13	Baseline calcium on $Kout_{Ca}$ *(piece-wise linear)*	15546.92	15542.33	4.60	3.84	1	0.032

OFV_{OLD} : OFV before covariate is added
OFV_{NEW} : OFV after covariate is added
d.f.: Degree of freedom
"*linear*" and "*piece-wise linear*" in parentheses represent linear and piece-wise linear covariate-parameter relationship, respectively.

Table 5. Covariates deleted at each step (Backward deletion)

	Covariate	OFV_{OLD}	OFV_{NEW}	ΔOFV	Criterion	d.f.	P-value
Step 1	Weight on $Kout_{Ca}$ *(by linear)*	15542.33	15546.89	4.56	6.63	1	0.03265
Step 2	Baseline calcium on $Kout_{Ca}$ *(by linear)*	15546.89	15551.82	4.93	6.63	1	0.02645
Step 3	Weight on $K_{R,Ca}$	15551.82	15556.54	4.72	6.63	1	0.02978

OFV_{OLD} : OFV before covariate is deleted
OFV_{NEW} : OFV after covariate is deleted
d.f.: Degree of freedom

The model selected was then refined by deleting covariate coefficients the confidence interval of which includes 0. Here, sup-groups having loss of three parathyroid glands and regional neck dissection merged with neighboring sub-groups to avoid numerical instability due to a small number of subjects belonging to each group. As a result, the effect of baseline PTH on $K_{R,Ca,}$ was deleted.

The refined model, which is the final model, shows that $Kout_{Ca}$ increases with body weight and radical neck dissection and it decreases with baseline calcium level, $K_{R,Ca}$ decreases with total surgical removal of thyroid, and Amp_p increases with baseline PTH, total thyroidectomy, number of loss of PTG and old age . Mathematically,

$$Kout_{Ca} = KOUTC_{BASIC}*(1 + COV1*(WT - WT_{MEDIAN}))*(1 + COV2)*(1 + COV3*(Ca0 - Ca0_{MEDIAN}))$$

$KOUTC_{BASIC}$ = THETA(9)

COV1 = THETA(26)

WT_{MEDIAN} = 60

COV2 = THETA(24) for ND = None

COV2 = 0 for ND = CCND

COV2 = THETA(23) for ND = MRND and regional

COV3 = THETA(21)

$Ca0_{MEDIAN}$ = 9.1

$K_{R,Ca,}$ = $KRCA_{BASIC}$*(1 + COV4)

$KRCA_{BASIC}$ = THETA(5)

COV4 = 0 for OPTYPE = Total thyroidectomy

COV4 = THETA(29) for OPTYPE = Subtotal thyroidectomy

COV4 = THETA(28) for OPTYPE = Hemithyroidectomy

Amp_p = Amp_p_{BASIC} *(1 + COV5*(PTH0 - $PTH0_{MEDIAN}$))*(1 + COV6)*(1 + COV7)*(1 + COV8*(AGE - AGE_{MEDIAN}))

Amp_p_{BASIC} = THETA(4)

COV5 = THETA(20)

$PTH0_{MEDIAN}$= 46.1

COV6 = 0 for PTGLOSS = 0

COV6 = THETA(17) for PTGLOSS = 1

COV6 = THETA(18) for PTGLOSS = 2,3

COV7 = 0 for OPTYPE = Total thyroidectomy

COV7 = THETA(16) for OPTYPE = Subtotal thyroidectomy

COV7 = THETA(15) for OPTYPE = Hemithyroidectomy

COV8 = THETA(14)

AGE_{MEDIAN}= 43

The estimates of the refined final model parameters and bootstrap results are shown in **Table 6**. The medians of bootstrap estimates were close to the estimates from the final model.

Table 6. Parameter estimates and bootstrap results for the final model

Model parameters (unit)		Parameter estimates (%RSE)	Bootstrap median (90% CI)	Shrinkage (%)
Structural model				
Ca(0) (mg/dL)	THETA(1)	9.17 (0.240)	9.17 (9.14 - 9.20)	
PTH(0) (pg/mL)	THETA(2)	46.8 (1.97)	47.0 (45.5 – 48.2)	
$Kout_{Ca}$ = $KOUTC_{BASIC}$*(1 + COV1*(WT - WT_{MEDIAN}))*(1 + COV2)*(1 + COV3*(Ca0 - $Ca0_{MEDIAN}$))				
$KOUTC_{BASIC}$ (/day)	THETA(9)	0.130 (3.98)	0.130 (0.121 – 0.140)	
COV1	THETA(26)	-0.00522 (29.8)	-0.00519 (-0.00818 - -0.00169)	
COV2 for ND = None	THETA(24)	-0.136 (148)	-0.136 (-0.28 – 0.0548)	
COV2 for ND = CCND		0 fix	0 fix	
COV2 for ND = MRND and regional	THETA(23)	0.215 (33.9)	0.215 (33.9)	

COV3	THETA(21)	-0.250 (24.3)	-0.275 (-0.379 - -0.106)
$Kout_{PTH}$ (/day)	THETA(10)	0.930 (1.90)	0.943 (0.872 – 0.981)
$K_{R,Ca}$ = $KRCA_{BASIC}$*(1 + COV4)			
$KRCA_{BASIC}$ (/day)	THETA(5)	0.811 (8.92)	0.814 (0.714 – 0.943)
COV4 for OPTYPE = Total thyroidectomy		0 fix	0 fix
COV4 for OPTYPE = Subtotal thyroidectomy	THETA(29)	0.508 (44.8)	0.539 (0.114 – 0.943)
COV4 for OPTYPE = Hemithyroidectomy	THETA(28)	2.25 (24.1)	2.27 (1.88 – 2.99)
$K_{R,PTH}$ (/day)	THETA(6)	0.606 (3.08)	0.943 (0.872 – 0.981)
V (L)	THETA(12)	2350 (15.7)	2390 (13500 - 40700)
m		0.0398 fixed	0.0398 fixed
l	THETA(13)	0.223 (20.4)	0.257 (0.171 – 0.394)

Amp_c (mg/dL)	THETA(3)	0.223 (18.7)	0.224 (0.172 – 0.285)

$Amp\_p = Amp\_p_{BASIC} *(1 + COV5*(PTH0 - PTH0_{MEDIAN}))*(1 + COV6)*(1 + COV7)*(1 + COV8*(AGE - AGE_{MEDIAN}))$

Amp_p_{BASIC} (pg/mL)	THETA(4)	14.3 (7.45)	14.6 (13.0 – 16.3)
COV5	THETA(20)	0.0122 (21.4)	0.0109 (0.00608 – 0.0161)
COV6 for PTGLOSS = 0		0 fix	0 fix
COV6 for PTGLOSS = 1	THETA(17)	0.276 (37.9)	0.260 (0.147 – 0.406)
COV6 for PTGLOSS = 2,3	THETA(18)	0.586 (53.8)	0.586 (0.258 – 0.847)
COV7 for OPTYPE = Total thyroidectomy		0 fix	0 fix
COV7 for OPTYPE = Subtotal thyroidectomy	THETA(16)	-0.675 (13.9)	-0.667 (-0.790 - -0.559)
COV7 for OPTYPE =	THETA(15)	-0.663 (7.38)	-0.669 (-0.831 - -0.567)

Hemithyroidectomy				
COV8	THETA(14)	0.00920 (34.7)	0.00862 (0.00410 – 0.0141)	
Inter-individual Variability				
ω (*Ca(0)*) (%CV)		1.62 (9.02)	1.56 (0.770 – 2.13)	53.801
ω (*PTH(0)*) (%CV)		25.6 (5.31)	25.4 (23.3 – 27.5)	11.574
ω ($Kout_{Ca}$) (%CV)		15.6 (20.9)	14.3 (6.25 – 20.0)	67.553
ω ($K_{R,Ca}$) (%CV)		58.4 (9.18)	58.9 (52.0 – 66.7)	37.552
ω (Amp_c) (%CV)		110 (13.3)	109 (96.8 - 125)	53.629
ω (Amp_p) (%CV)		29.3 (21.1)	27.8 (15.8 – 35.5)	59.601
Residual Variability				
$\sigma_{proportional\_Ca}$ (%CV)		4.63 (1.22)	4.63 (4.41 – 4.79)	10.026
$\sigma_{proportional\_PTH}$ (%CV)		31.6 (1.72)	31.6 (30.3 – 32.5)	7.9202

WT : body weight, ND : neck dissection, Ca0 : baseline calcium, PTH0 : baseline PTH, OPTYPE : type of thyroidectomy, PTGLOSS : parathyroid gland loss, COV : covariate coefficient

Figure 3 and **Figure 4** show goodness of fit plots for the final model of calcium and PTH levels, respectively. In **Figure 3** and **Figure 4**, the smooth line (red line) was close to the line of identity (a) and the line of zero residual value (b and c), indicating the model describes the data adequately. The only exception is **Figure 4(b)**, which shows a slight overestimation beyond 300 days.

To further evaluate the model predictability, VPCs for the final model of calcium (left) and PTH (right) levels are plotted in **Figure 5**, where the prediction interval was set to 80%, instead of 95%, due to sparseness of the data. Fluctuations of observations and resulting misfits seen in that figure become less obvious when plotted up to 90 days in **Figure 6** and almost disappear with the model prediction matching with observations well when plotted up to 20 days in **Figure 7**. This indicates that the misfits observed in **Figure 5** resulted from sparseness of the data at the middle and later periods of observation.

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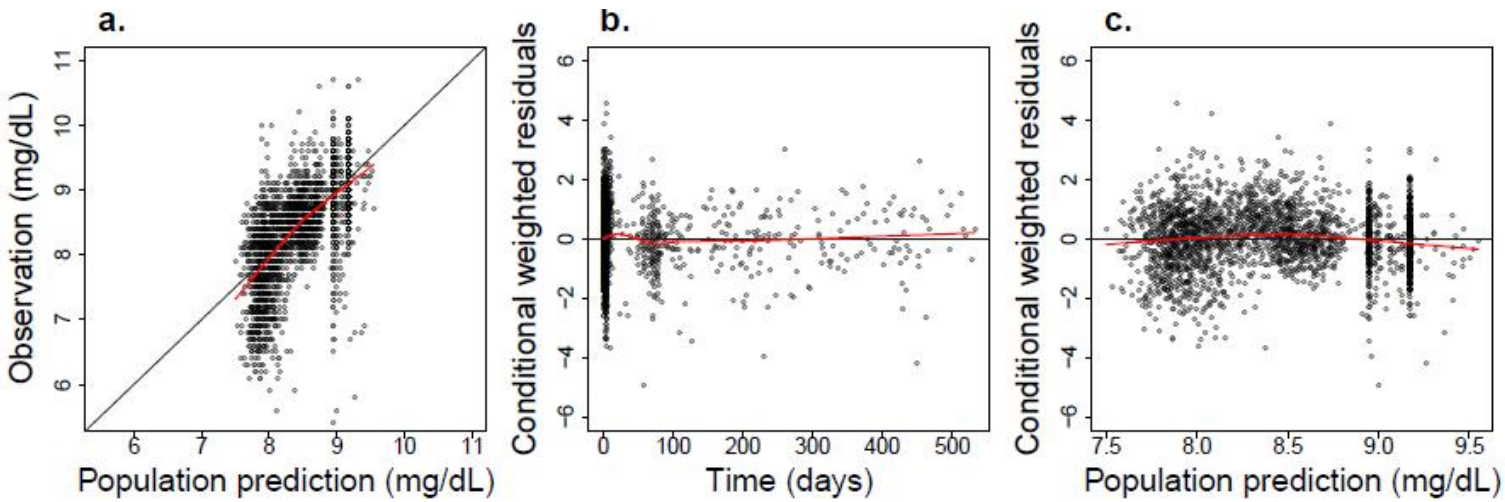


Figure 3. **Goodness of fit plot of the final model (Calcium concentration). a**. Observations vs. population model predictions, **b**. The conditional weighted residuals vs. time and **c**. The conditional weighted residuals vs. population model predictions. The black dots represented the observations, the grey line represented the line of identity (a) and the line of zero residual value (b and c) and the red line represented the smoother line.

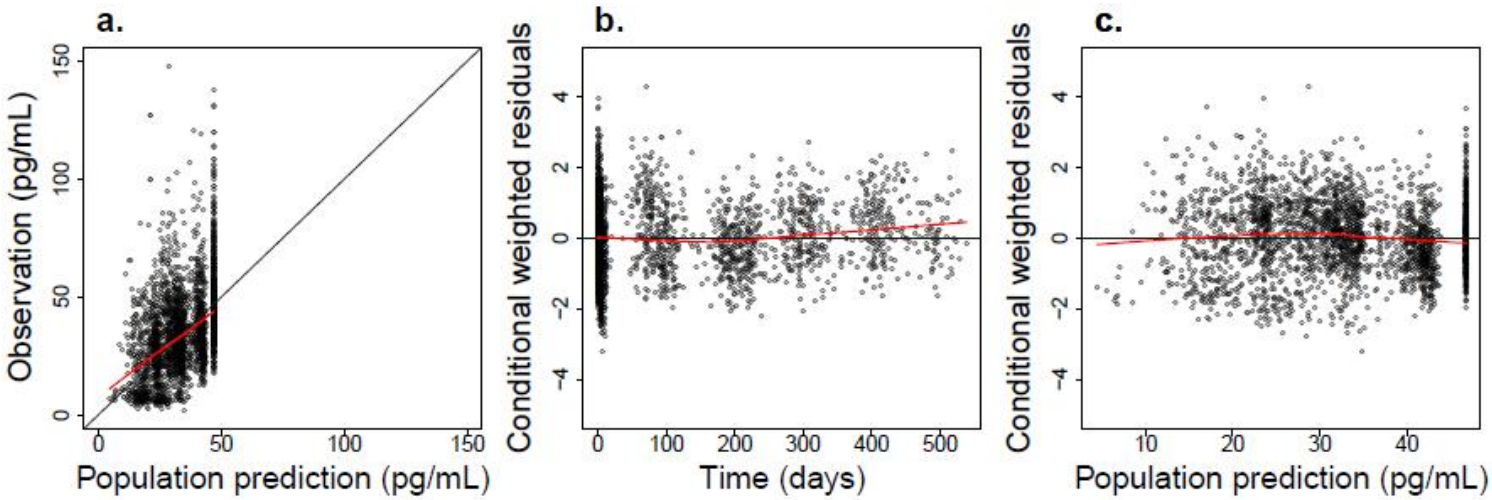


Figure 4. **Goodness of fit plot of the final model (PTH concentration). a**. Observations vs. population model predictions, **b**. The conditional weighted residuals vs. time and **c**. The conditional weighted residuals vs. population model predictions. The black dots represented the observations, the grey thin line represented the line of identity (a) and the line of zero residual value (b and c) and the red line represented the smoother line.

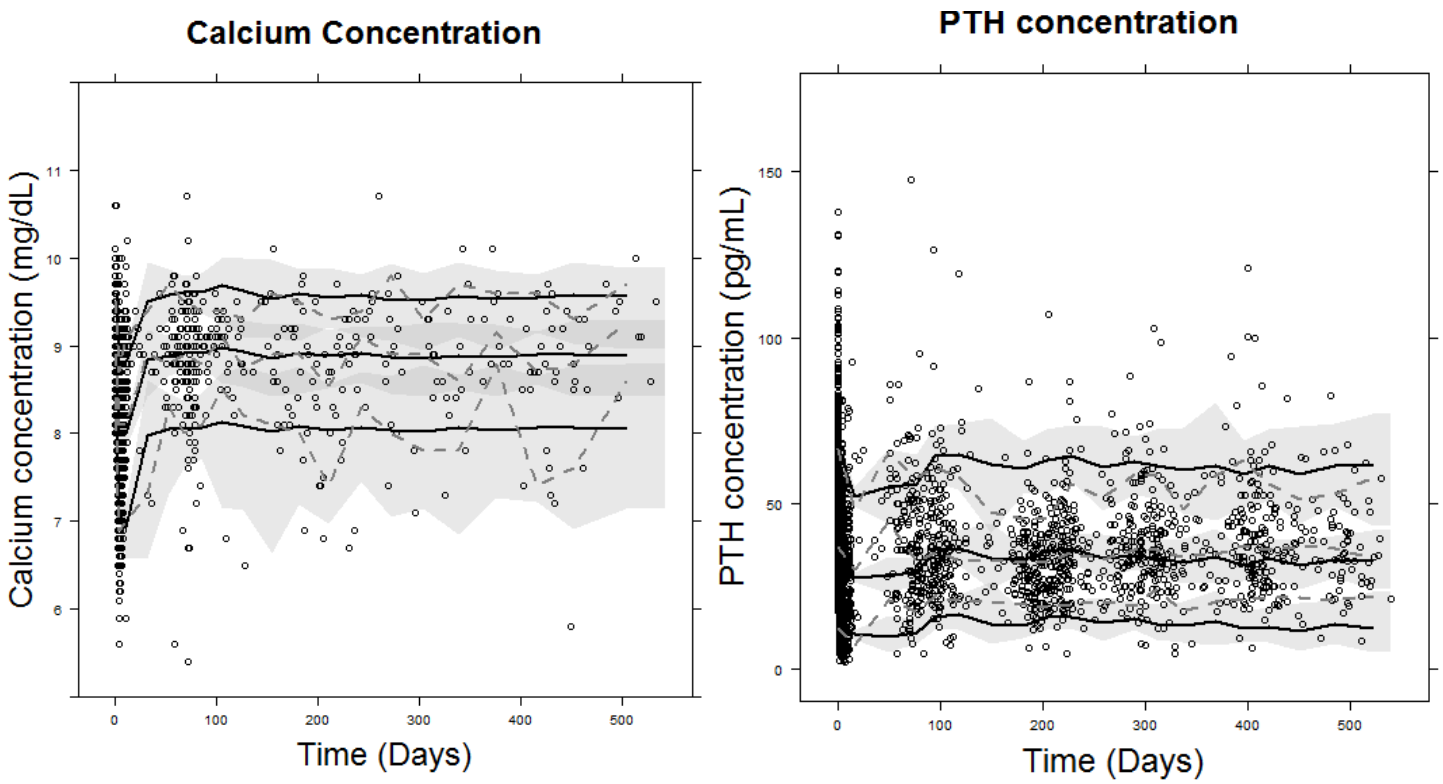


Figure 5. **VPC plots of the final model (Calcium concentration (left) and PTH concentration (right)).** The observed data (*black dots*) were plotted with the 10th, 50th and 90th percentiles of the observations (*grey dashed lines*) and predictions (dark *grey solid lines*) were plotted with the 95% confidence interval (shaded areas).

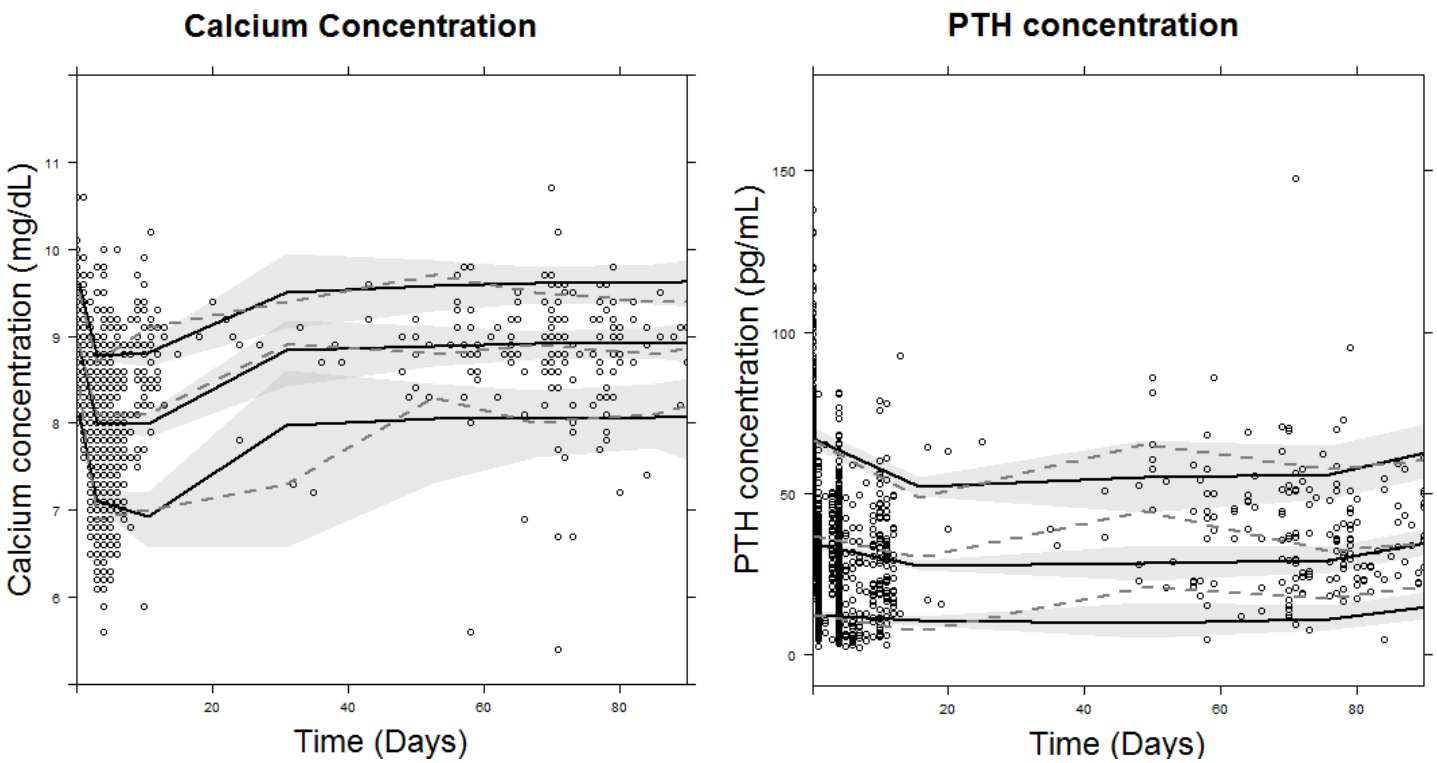


Figure 6. **VPC plots of the final model up to 90 days (Calcium concentration (left) and PTH concentration (right)).** The observed data (*black dots*) were plotted with the 10th, 50th and 90th percentiles of the observations (*grey dashed lines*) and predictions (dark *grey solid lines*) were plotted with the 95% confidence interval (shaded areas).

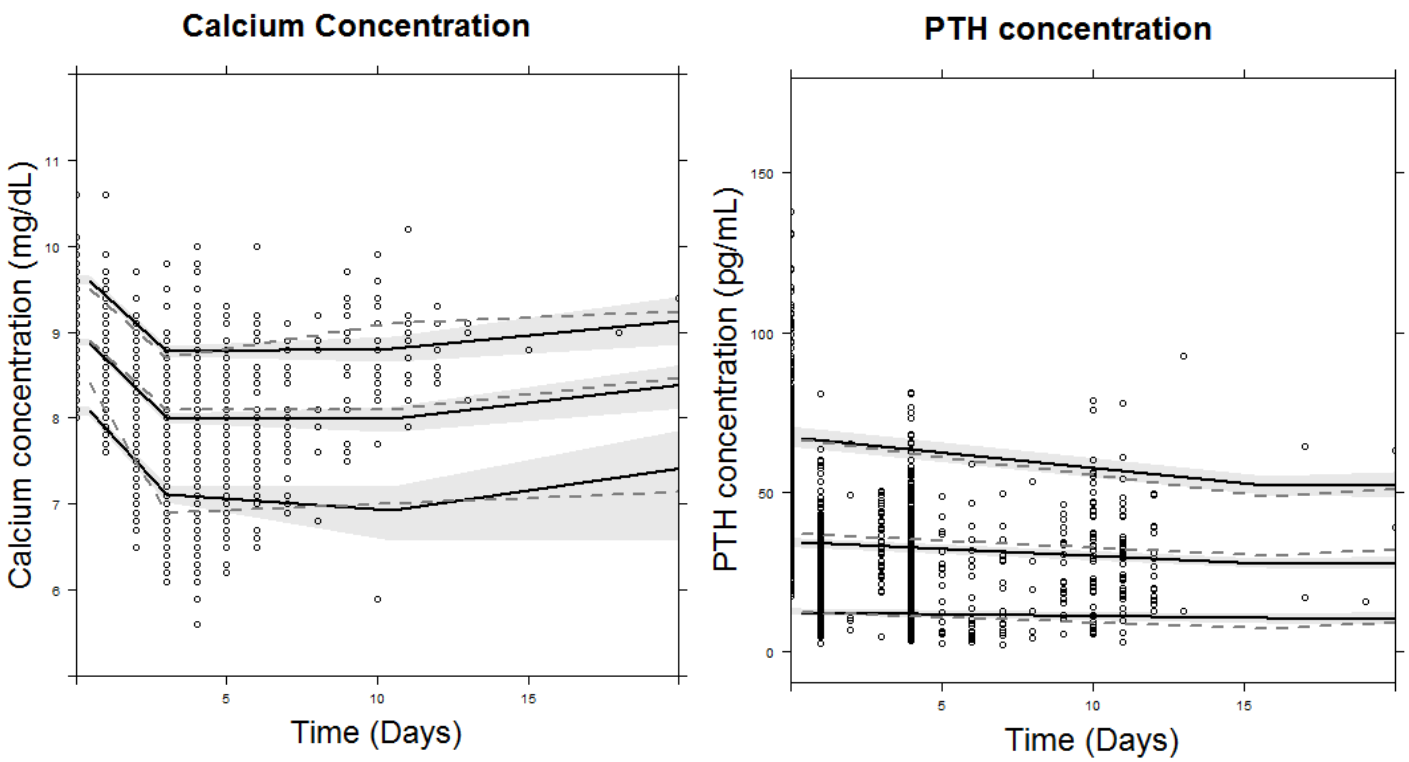
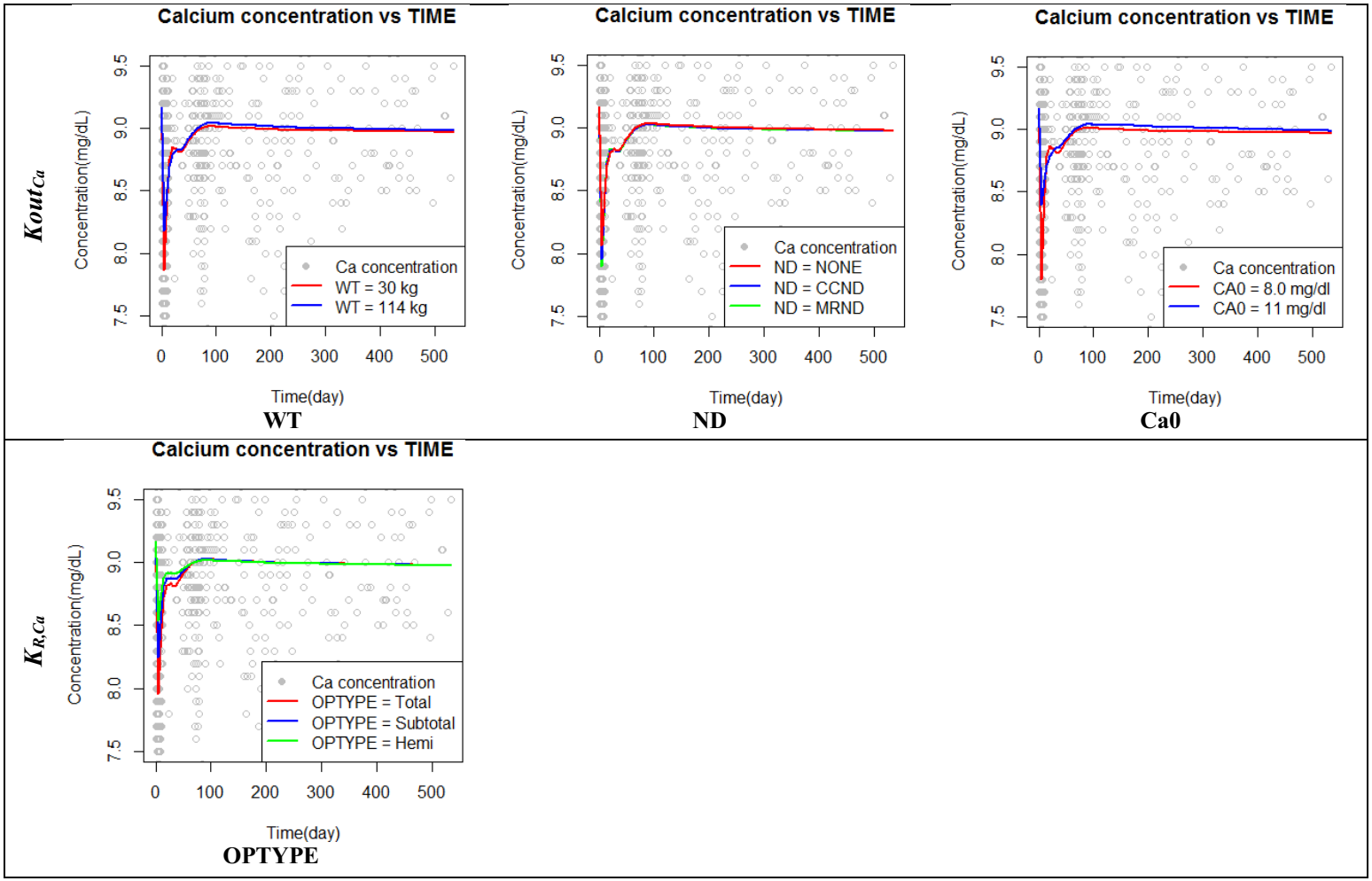


Figure 7. VPC plots of the final model up to 20 days (Calcium concentration (left) and PTH concentration (right)). The observed data (*black dots*) were plotted with the 10th, 50th and 90th percentiles of the observations (*grey dashed lines*) and predictions (dark *grey solid lines*) were plotted with the 95% confidence interval (shaded areas).

The difference in calcium and PTH time courses predicted from the final model (**Table 6)** between covariate subgroups is presented in **Figure 8**, where the model prediction was obtained by setting the values of all other covariates, except for the one under evaluation, to median values for continuous covariates and the most common subgroup for categorical covariates. In continuous covariates of body weight, baseline calcium level and age, minimum and maximum values were used to show maximum difference between subgroups

Figure 8 shows that, for the influence of the covariate of $Kout_{Ca}$, the maximum decrease of calcium concentration decreases with body weight, increases with the severity of neck dissection and decreases with baseline calcium level, and, for the influence of the covariate of $K_{R,Ca}$, the maximum decrease of calcium concentration increases with the extent of surgery, with total thyroidectomy yielding the largest decrease. For the influence of the covariate of Amp_p, the decrease of PTH concentration increases with the number of loss of PTG, the extent of surgery and age.


Calcium concentration vs TIME
Concentration(mg/dL)
Time(day)
Ca concentration
WT = 30 kg
WT = 114 kg
WT
Calcium concentration vs TIME
Concentration(mg/dL)
Time(day)
Ca concentration
ND = NONE
ND = CCND
ND = MRND
ND
Calcium concentration vs TIME
Concentration(mg/dL)
Time(day)
Ca concentration
CA0 = 8.0 mg/dl
CA0 = 11 mg/dl
Ca0
Kout_Ca
Calcium concentration vs TIME
Concentration(mg/dL)
Time(day)
Ca concentration
OPTYPE = Total
OPTYPE = Subtotal
OPTYPE = Hemi
OPTYPE
K_R,Ca

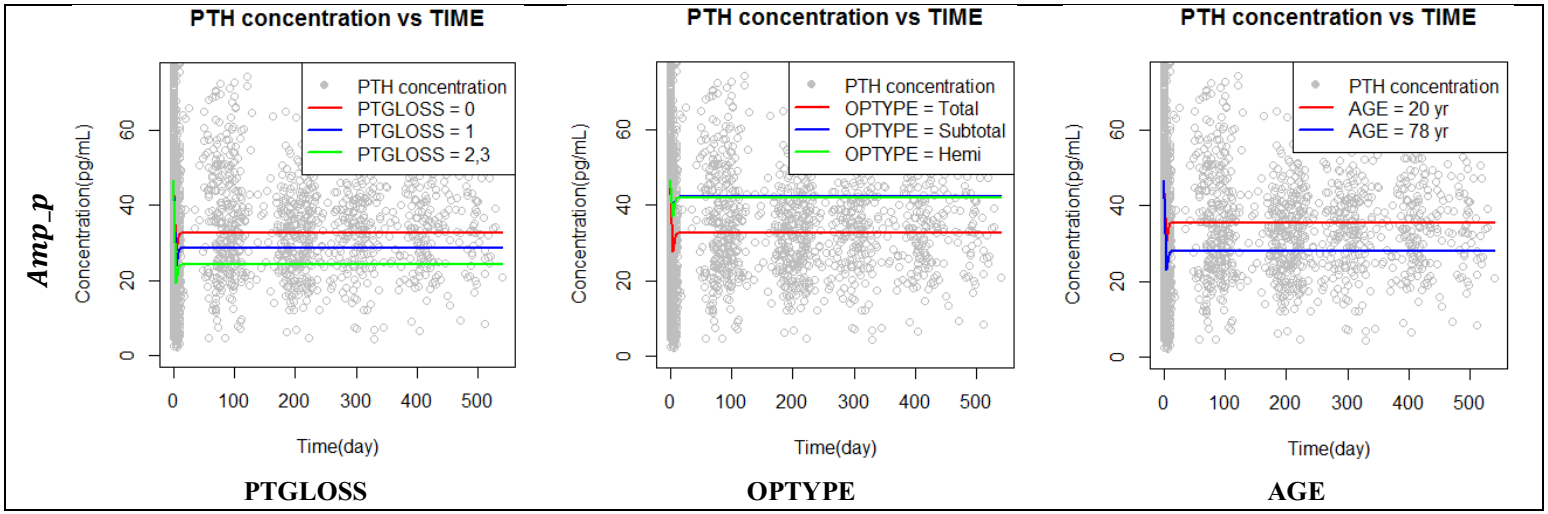


Figure 8. **The difference in calcium and PTH time courses for covariate subgroups.** The grey dots represent the observations, and solid smooth lines represent population predictions of each subgroup. WT : body weight, ND : neck dissection, Ca0 : baseline calcium, OPTYPE : type of thyroidectomy, PTGLOSS : parathyroid gland loss

IV. DISCUSSION

In this study, a quantitative model of calcium and parathyroid hormone level changes after thyroidectomy in Korean population was developed based on the disease progression model concept. Basically, turnover model was used to describe the homeostasis and feedback loop of the calcium and PTH based on known physiological knowledge.[20] Though there have been several quantitative attempts to model calcium physiology,[22-25] to my knowledge, the model presented here is the first targeted on the patients after thyroidectomy, especially in Korean population.

The model for CaSR was derived with some modifications from the model developed by *Abraham et al.*[22] But it was not exactly same as the cited model. In our model, the slope parameter for the negative feedback via CaSR (m) was chosen to be unrelated to the baseline PTH level ($PTH(0)$) because being related to $PTH(0)$did not improve the model and increased model instability. As in *Abraham et al.,* we also had difficulty estimating m and had to fix m at a value obtained from initial successful run.

While *Abraham et al.* did not include the effect of PTH on calcium level due to the short observation period,[22] *Satterwhite et al.* developed a pharmacokinetic-pharmacodynamic model for teriparatide, a recombinant human PTH (rhPTH) for osteoporosis treatment, incorporating calcium response during 24 hr after last dose.[24] In their work, a wide range of concentration data was obtained after daily injection of teriparatide and the authors modeled the effect of teriparatide using an E_{max} function.

In our data, however, the PTH levels were collected sparsely and the range of observed PTH level in one patient was not as wide as that of *Satterwhite et al.* To avoid difficulty in estimating especially the parameter representing the concentration required to produce 50% of maximum calcium increasing effect, simpler empirical function (Equation (11)) was used in our model and it worked well.

Abraham et al. also used precursor model to characterize PTH turnover.[22] It was physiologically reasonable because PTH is synthesized via proteolytic cleavages from precursor polypeptides.[46] However the model with virtual precursor compartment was largely unstable and needed huge computing time. The discrepancy between the scale of PTH formation kinetics and PTH level observation interval was considered as a possible cause of failed precursor model. In *Abraham et al.*'s study, blood samples were withdrawn at 5 – 10 min intervals.[22] But in our study, the observation time unit was a day.

Transient decreases of calcium and PTH levels were common after thyroidectomy. There were some possible reasons for the Transient decrease of calcium and PTH; hemodilution during operation, calcitonin release in thyroid gland manipulation, hungry bone syndrome with hyperthyroidism osteodystrophy and transient injury, including devascularization of parathyroid gland.[6-9] According to the parameter estimates of the basic model in **Table 2**, this transient operation effect disappeared within 2 ~ 4 days. Because this transient effect indirectly resulted from the operation, there was a delay in the response.[47,48] This model suggested that 3.5 wk would be needed to reach new steady-state of calcium and PTH levels.

Incomplete recovery function was added to describe patients who were not fully recovered from decreased calcium and/or PTH level. The inter-individual variabilities of amplitude of incomplete recovery were about 100% and 50% in calcium and PTH (**Table 2**). It indicated that the model improvement could be possible after identifying influencing factors.

Despite a strong correlation with the type of thyroidectomy ($p<0.0001$, not shown), Amp_c was not tested due to possible confounding effects with vitamin D supplements externally given to recover decreased calcium levels.

Among the potential influencing factors, the type of thyroidectomy was the most significant factor on $Kout_{Ca}$, $K_{R,Ca}$, and Amp_p ($p < 10^{-30}$). The level of neck dissection was also highly related to $Kout_{Ca}$, $K_{R,Ca}$, and Amp_p ($p < 0.001$) (**Table 3**). It could be interpreted that the amount of tissue removed is the most predictable factor to the time course of calcium level after thyroidectomy.

The refined model, which is the final model, shows that $Kout_{Ca}$ increases with body weight and radical neck dissection and it decreases with baseline calcium level, $K_{R,Ca}$ decreases with total surgical removal of thyroid, and Amp_p increases with baseline PTH, total thyroidectomy, number of loss of PTG and old age (**Table 6** and **Figure 8).** Except for the $Kout_{Ca}$ – body weight relationship, the other selected parameter-covariate relationships were consistent with the preliminary analysis results in **Table 3** and previous papers.[5-7,13-19,49] In the previous studies, body weight was not a potential influencing factor to be tested. Instead, sex was tested and female gender

showed a significance impact on hypocalcemia. [6,14,18] In our data, body weight was significantly different between male and female (p = 8.90e-29) and the significance of the $Kout_{Ca}$ – sex relationship dramatically became insignificant when the $Kout_{Ca}$ – weight relationship was included at Step 7 of forward selection step (p = 0.006556 for step 7 and p=0.2246 for step 8). It might suggest that the well-known influence of female gender on hypocalcemia was derived from the difference in body weights.

The 25-OH-vitamin D was known as one of the significant factors on the symptomatic hypocalcemia after total hyroidectomy.[50] However, in this study, it was not selected as a significant covariate. We conjectured that it was due to the large amount of missing information (457 of 1,142 subjects have no information on 25-OH-vitamin D) which was treated as median value in the covariate model building. If the analysis is done by excluding subjects with missing values, the result could change and become consistent with the previous study.

Because the model developed in this work is rather complex, a user-friendly software application if available would be of help for clinicians who are not familiar with mathematical models to understand capabilities of the developed model and apply them in clinical situations. **Figure 9** shows the simulated result based on the final model using the application developed by R and the shiny package.[45] It illustrates that users can easily generate model predictions for various combinations of covariate values using sliders, radio buttons and selection boxes, etc.

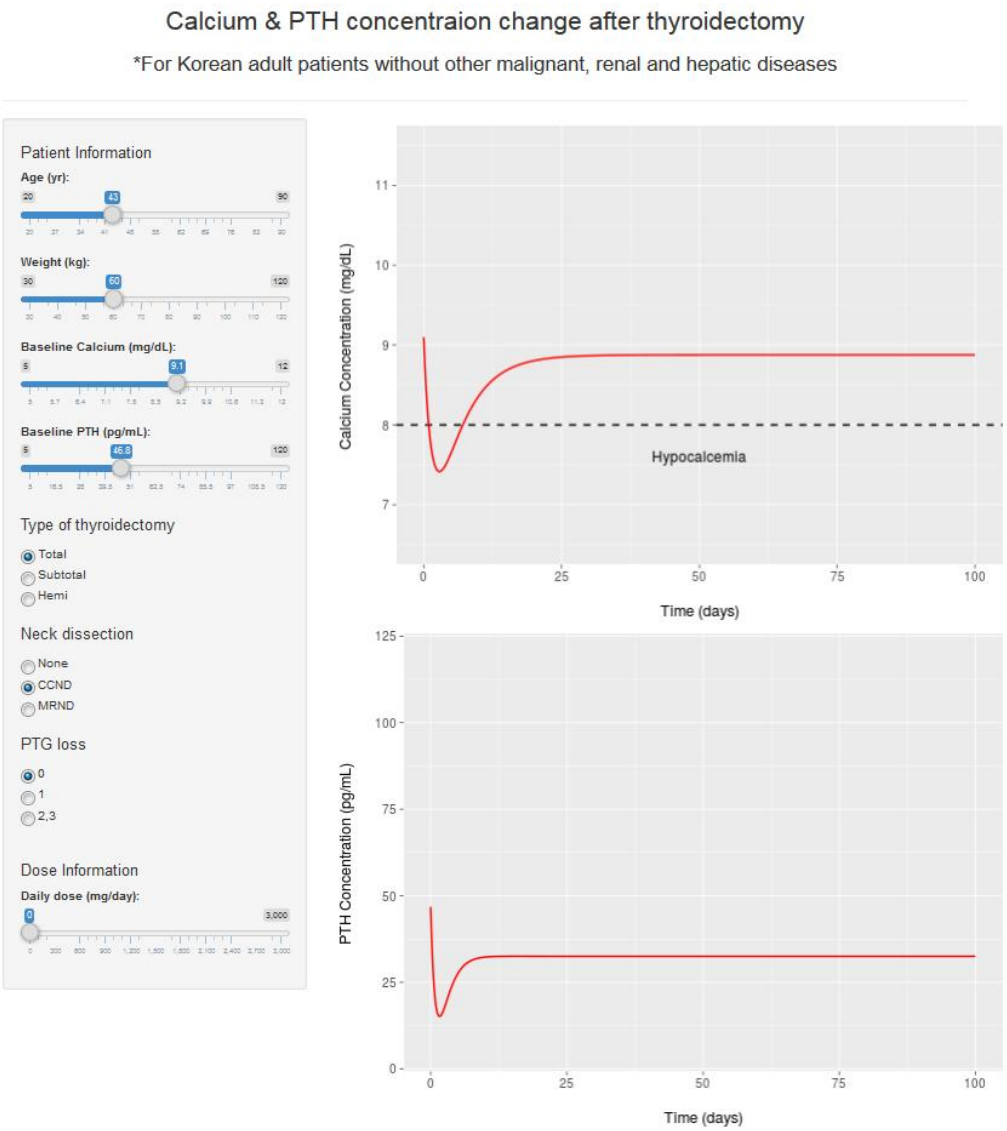


Figure 9. Snapshot of an output of an application software generating model predictions for calcium and PTH level changes after thyroidectomy and calcium supplements intake in Korean adult population. The application was developed using R and Shiny package and available at the web page: https://uhhauhha.shinyapps.io/app-6/.

Though the routine clinical data has a merit in representing real-world patients, the limitations also exist in characterizing the data as seen in our study; bias was inevitable in retrospective data collection due to incomplete dose information on calcium supplement administration.

Once the final model is validated properly, it could be used as a tool to predict the post-operative time-course of calcium and PTH level changes in Korean population receiving thyroidectomy.

V. CONCLUSION

Although there are other modeling approaches available, this is the first model quantitatively describing the calcium and PTH level changes after thyroidectomy in Korean population based on known physiology. With successful validation, this model could be used as a supportive tool in efficient management of calcium and PTH levels after thyroidectomy in Korean population.

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ABSTRACT (IN KOREAN)

한국인에서 갑상선 절제술이 칼슘 농도에 미치는 영향과 칼슘 보조제 효과의 예측 모형

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손 미 정

갑상선절제술은 한국뿐 아니라 미국 등 세계적으로 매우 높은 빈도로 수행되는 수술의 하나이다. 저칼슘혈증은 갑상선절제술 후 가장 많이 나타나면서도 중요한 부작용 중에 하나로, 술 후 환자의 재원 기간의 증가와 삶의 질 저하를 가져올 수 있다. 현재까지 술 후 저칼슘혈증이 일어나는 환자를 예측하기 위하여 많은 연구가 이루어졌으나 주로 특정 시기에서의 칼슘농도를 영향 인자에 따라 서로 비교하는 것에 그치고 있으며

갑상선 절제술 후 시간에 따른 칼슘 농도의 변화를 예측하는 종적연구는 찾을 수 없었다. 이러한 배경을 바탕으로 본 연구는 한국인에서 갑상선 절제술 후 시간에 따른 칼슘 농도의 변화와 저칼슘혈증의 치료에 사용되는 칼슘 보조제의 효과를 예측하는 모형을 개발하여 효과적인 술 후 저칼슘혈증 관리에 도움이 될 것을 목적으로 한다.

본 연구는 한국인 표준모형을 개발하는 연구로써, 연세의료원 신촌 세브란스병원 외과에서 2013년 1월부터 2013년 6월 사이의 기간에 갑상선 절제술을 받은 20세 이상의 한국인 환자들을 대상으로 갑상선 절제술 후의 칼슘 보조제 투약 정보 및 칼슘과 부갑상선 호르몬 농도의 시계열 자료, 문헌조사를 통해 선정한 칼슘 농도에 영향을 미칠 것으로 기대되는 인자들에 대한 정보를 얻어 분석하였다. 이 중 갑상선 절제술의 과거력이 있는 대상자와 술전 칼슘 및 부갑상선호르몬 수치가 없는 대상자는 제외하였으며, 유사저칼슘혈증 (pseudohypocalcemia)를 나타낼 수 있는 저알부민혈증의 가능성이 있는 질환 (간경변, 신질환, 암 등)을 가진 경우도 제외하였다.

질병진행모형(disease progression model) 개념을 바탕으로, 일상적 임상자료(routine clinical data)의 분석에 유용한 비선형혼합효과모형을 사용하여 모형이 구축되었다. 기본적으로 turnover model을 사용하여 항상성을 가진 내인성 인자인 칼슘 및 부갑상선 호르몬의 기저모형을 구현하였고, 알려진 생리적 현상인 칼슘-부갑상선 호르몬 피드백 메카니즘을

추가함으로써 모형을 개선할 수 있었다. 여기에 술 후 급격하게 떨어졌다가 회복되는 칼슘 및 부갑상선 호르몬의 초기 추세와 일부 환자에서 후반부까지 지속되는 칼슘 및 부갑상선 호르몬의 감소를 각각 갑상선 절제술의 초기 및 후기 효과로 반영하였다. 칼슘 보조제를 투약 받은 경우, 하루에 투여하는 칼슘의 총량만큼 일정한 속도로 혈중 칼슘농도를 직접 증가시키는 모형으로 그 효과를 정량화 할 수 있었다.

공변량 분석 후 최종 모형에서 체중, 경부청소술 (neck dissection) 범위 와 술 전 칼슘 농도가 $Kout_{Ca}$ 와, 갑상선 절제술의 종류가 $K_{R,Ca}$ 와 관련 있었으며, 술 전 부갑상선 호르몬 농도, 제거된 부갑상선의 개수, 갑상선 절제술의 종류, 나이가 Amp_p 와 관련 있었다.

최종모형은 Akaike information criterion (AIC), goodness of fit, visual predictive check, bootstrap 등을 통해 평가되었고 이에 따라 최종 모델이 자료를 잘 설명한다고 판단할 수 있었다.

향후 충분한 타당성의 검증이 이루어진다면, 본 연구를 통해 최종적으로 제안된 모형을 통해 갑상선 절제술 후 시간에 변화하는 칼슘 농도와 이에 영향을 미치는 인자들 및 칼슘 보조제의 효과를 예측함으로써 효과적인 술 후 칼슘 농도 관리에 도움이 될 수 있을 것으로 기대된다.

핵심되는 말: 갑상선절제술, 저칼슘혈증, 칼슘, 칼슘 보조제, 비선형혼합효과모형, 질병진행모형