Analysis of time course and dose effect from metformin on body mass index in children and adolescents

Dong-Dong Wang[1,*], Yi-Zhen Mao[2,*], Su-Mei He[3], Xiao Chen[1,4,5]

[1]Jiangsu Key Laboratory of New Drug Research and Clinical Pharmacy, School of Pharmacy, Xuzhou Medical University, Xuzhou, Jiangsu 221004, China;
[2]Department of Endocrinology, Xuzhou Central Hospital, Xuzhou, Jiangsu 221009, China;
[3]Department of Pharmacy, The Affiliated Suzhou Science & Technology Town Hospital of Nanjing Medical University, Suzhou Jiangsu, 215153, China;
[4]Department of Pharmacy, The People's Hospital of Jiangyin, Jiangyin Jiangsu, 214400, China;
[5]Department of Pharmacy, Children's Hospital of Fudan University, Shanghai, 201102, China;

*Contributed equally.
Correspondence:
Dong-Dong Wang, Jiangsu Key Laboratory of New Drug Research and Clinical Pharmacy, School of Pharmacy, Xuzhou Medical University, Xuzhou, Jiangsu 221004, China, Email address: 13852029591@163.com.
Su-Mei He, Department of Pharmacy, The Affiliated Suzhou Science & Technology Town Hospital of Nanjing Medical University, Suzhou Jiangsu, 215153, China, Email address: hehe8204@163.com.
Xiao Chen, Department of Pharmacy, The People's Hospital of Jiangyin, Jiangyin Jiangsu, 214400, China, Email address: chenxiao112733@163.com.

Abstract
The purpose of this study was to analyze the time course and dose effect from metformin on body mass index (BMI) in children and adolescents by model-based meta-analysis (MBMA). Searching randomized controlled trial (RCT) studies of metformin on BMI in children and adolescents. The change rates of BMI from baseline values were used to evaluate metformin efficacy indicator. A total of 18 RCT studies, 1228 children and adolescents, were included for analysis, including patients with obesity, patients with type 1 diabetes mellitus, patients with nonalcoholic fatty liver, patients with precocity. In order to achieve better effect of metformin on BMI in children and adolescents, the present study recommended that for patients with obesity, 1000 mg/day metformin was required for at least 15.2 weeks, and 60.8 weeks to achieve the plateau of metformin effect; For patients with type 1 diabetes mellitus, 1000 mg/day metformin was required for at least 25.2 weeks, and 100.8 weeks to achieve the plateau of metformin effect; For patients with nonalcoholic fatty liver,

1000 mg/day metformin was required for at least 6.57 weeks, and 26.28 weeks to achieve the plateau of metformin effect; For patients with precocity, 425 mg/day metformin was required for at least 12.4 weeks, and 49.6 weeks to achieve the plateau of metformin effect. It was the first time to analyze the time course and dose effect from metformin on BMI and to recommend dosage and duration of treatment for metformin in children and adolescents with different disease types.

Keywords: time course, dose effect, metformin, body mass index, children and adolescents

1 Introduction

Metformin was widely used in the control of weight in different diseases of children and adolescents(Kendall et al., 2013; Pastor-Villaescusa et al., 2017). For example, patients with obesity(Atabek and Pirgon, 2008; Burgert et al., 2008; Love-Osborne et al., 2008; Clarson et al., 2009; Wilson et al., 2010; Yanovski et al., 2011; Gomez-Diaz et al., 2012; Kendall et al., 2013; van der Aa et al., 2016; Garibay-Nieto et al., 2017; Pastor-Villaescusa et al., 2017), patients with type 1 diabetes mellitus(Codner et al., 2013; Nadeau et al., 2015; Nwosu et al., 2015), patients with nonalcoholic fatty liver(Nadeau et al., 2009; Lavine et al., 2011), and patients with precocity(Ibanez et al., 2006a; Ibanez et al., 2006b). Metformin controlled weight mainly through decreasing caloric intake, including direct and indirect impacts on appetite regulation from the gastrointestinal side effects(Yerevanian and Soukas, 2019). In addition, metformin increased the peptide hormone growth/differentiation factor 15 (GDF15) circulating levels, lowering food intake and reducing body weight by means of the brain-stem-restricted receptor(Coll et al., 2020). However, the weight control of patients with metformin was off-label, lacking clinical dosage and duration of treatment recommendation. Especially, the time course, and dose effect of metformin on body mass index (BMI) in children and adolescents with different disease types were unclear.

Model-based meta-analysis (MBMA) was a new quantitative pharmacological tool and could quantify dose course and time effect of drug(Mould, 2012; Wu et al., 2017). In particular, it could implement accurate pharmacodynamic comparison from the same drug in different disease types(Dong et al., 2018), and realize clinical drug dosage and duration of treatment recommendation(Chen et al., 2020a; b; Cheng et al., 2020). The purpose of this study was to analyze the time course and dose effect from metformin on BMI using MBMA method and to recommend dosage and duration of treatment for metformin in children and adolescents with different disease types.

2 Methods

2.1 Literature search and data extraction

We retrieved the Pubmed database (https://pubmed.ncbi.nlm.nih.gov/) with the

deadline of September 2020. Only English publications were searched. Inclusion criteria included: (i) children and adolescents, (ii) metformin treatment, (iii) randomized controlled trial (RCT), (iv) placebo controlled trial, (v) with BMI information. Disease type, source, grouping, metformin dosage and duration of treatment, BMI, number of patient and age *et al* were extracted from the above included studies. History and search details were shown in the Supporting Material (Table S1). In order to eliminate the potential baseline effect, metformin efficacy (E) was evaluated using BMI change rate from baseline values in the present research. The formula (1) was as follows:

$$E\% = \frac{E_t - E_b}{E_b} \times 100\% \tag{1}$$

E_t, the value of BMI at time t; E_b, the value of BMI at baseline.

2.2 Model Establishment

In order to get actual drug effect on BMI form metformin, the placebo effect should be deducted from metformin group. In addition, E_{max} models were used to assess the effect of metformin on BMI in children and adolescents with different disease types, because the effect on BMI from metformin varied with time and reached a plateau. The formulas (2) and (3) were as follows:

$$E_{m, i, j} = E_{g, i, j} - E_{p, i, j} \tag{2}$$

$$E_{m, i, j} = \frac{E_{max, i, j} \times Time}{ET_{50, i, j} + Time} + \frac{\varepsilon_{i, j}}{\sqrt{\frac{N_{i, j}}{100}}} \tag{3}$$

$E_{g, i, j}$, the sum effect on BMI from metformin, including actual metformin effect and placebo effect; $E_{m, i, j}$, the actual metformin effect on BMI; $E_{p, i, j}$, the placebo effect on BMI. i, different studies; j, time point of every study. E_{max}, the maximal effect of metformin on BMI; ET_{50}, the treatment duration to reach half of the the maximal effect of metformin on BMI; $\varepsilon_{i, j}$, the residual error of study i with j time; $N_{i, j}$, the sample size in study i with time point j. $\varepsilon_{i, j}$ was weighted by sample size, assumed to be normally distributed, with a mean of 0 and variance of $\sigma^2/(N_{i,j}/100)$.

Additive error or exponential error models were used to describe the inter-study variability. The formulas (4)-(7) were as follows:

$$E_{max, i, j} = E_{max} + \eta_{1, i} \tag{4}$$
$$ET_{50, i, j} = ET_{50} + \eta_{2, i} \tag{5}$$
$$E_{max, i, j} = E_{max} \times \exp(\eta_{1, i}) \tag{6}$$
$$ET_{50, i, j} = ET_{50} \times \exp(\eta_{2, i}) \tag{7}$$

$\eta_{1, i}$, $\eta_{2, i}$ were the inter-study variabilities, when available, they would be added into E_{max}, and ET_{50}, respectively. $\eta_{1, i}$, $\eta_{2, i}$ were assumed to normally distributed, with a mean of 0 and variance of $\omega_{1, i}^2$, $\omega_{2, i}^2$, respectively.

When building the covariates models, categorical covariates and continuous covariates were evaluated by formulas (8) and (9)-(10):

$$P_p = P_T + COV \times \theta_c \tag{8}$$
$$P_p = P_T + (COV - COV_m) \cdot \theta_c \tag{9}$$
$$P_p = P_T \times (COV/COV_m)^{\theta_c} \tag{10}$$

COV, covariate; P_p, the parameter for a patient with a covariate value of COV; P_T, the typical value of the parameter; COV_m, the median value of covariable in the population. θ_c, a correction coefficient of the covariate to the model parameter.

The nonlinear mixed effect modeling (NONMEM, edition 7, ICON Development Solutions, Ellicott City, MD, USA) was used to build models. After a basic model was built, potential covariates were considered to add into E_{max}. Objective function value (OFV) changes were assessed and as the covariate inclusion criteria. The decrease from OFV was greater than 3.84 (χ^2, α = 0.05，d.f. = 1), which was considered sufficient for inclusion; The increase of OFV was greater than 6.63 (χ^2, α = 0.01，d.f. = 1), which was considered sufficient for significance in the final model.

2.3 Model validation and prediction
The final model accuracy was evaluated by visual inspection of routine diagnostic plots (individual predictions *vs* observations). Prediction-corrected visual predictive check plots were used to assess the predictive performance of final models. The efficacy prediction from metformin on BMI in children and adolescents with different disease types were simulated by monte carlo method.

3 Results
3.1 Included studies
The process of literature search and details of included studies were shown in Figure 1 and Table 1, respectively. A total of 18 RCT studies, 1228 children and adolescents, were included for analysis, in which 11 studies for patients with obesity(Atabek and Pirgon, 2008; Burgert et al., 2008; Love-Osborne et al., 2008; Clarson et al., 2009; Wilson et al., 2010; Yanovski et al., 2011; Gomez-Diaz et al., 2012; Kendall et al., 2013; van der Aa et al., 2016; Garibay-Nieto et al., 2017; Pastor-Villaescusa et al., 2017), 3 studies for patients with type 1 diabetes mellitus(Codner et al., 2013; Nadeau et al., 2015; Nwosu et al., 2015), 2 studies for patients with nonalcoholic fatty liver(Nadeau et al., 2009; Lavine et al., 2011), 2 studies for patients with precocity(Ibanez et al., 2006a; Ibanez et al., 2006b). In addition, in the included studies, the dosage ranges of metformin in patients with obesity were 1000 mg/day-2000 mg/day, in patients with type 1 diabetes mellitus were 1000 mg/day-1700 mg/day, in patients with nonalcoholic fatty liver were 1000 mg/day-1700 mg/day, in patients with precocity were 425 mg/day-850 mg/day, respectively.

3.2 Modeling
The actual drug effect on BMI form metformin in children and adolescents with different disease types were shown in Table 2, the E_{max} of metformin on BMI in patients with obesity, patients with type 1 diabetes mellitus, patients with nonalcoholic fatty liver, patients with precocity were -10%, -4.31%, -4.7%, and -9.41%, respectively. The ET_{50} of metformin on BMI in patients with obesity, patients with type 1 diabetes mellitus, patients with nonalcoholic fatty liver, patients with

precocity were 15.2 weeks, 25.2 weeks, 6.57 weeks, and 12.4 weeks, respectively. In addition, no covariate (in particular dosage) was incorporated into the E_{max} models, showing there was no significant dose dependence from metformin efficacy on BMI in children and adolescents with different disease types from the current included studies.

The E_{max} models of metformin on BMI in patients with obesity, patients with type 1 diabetes mellitus, patients with nonalcoholic fatty liver, patients with precocity were shown in formulas (11)-(14), respectively:

$$E = \frac{-10\% \times \text{Time}}{15.2 + \text{Time}} \tag{11}$$

$$E = \frac{-4.31\% \times \text{Time}}{25.2 + \text{Time}} \tag{12}$$

$$E = \frac{-4.7\% \times \text{Time}}{6.57 + \text{Time}} \tag{13}$$

$$E = \frac{-9.41\% \times \text{Time}}{12.4 + \text{Time}} \tag{14}$$

E, efficacy of metformin on BMI; Time, metformin treatment duration.

3.3 Validation

The visual inspection of routine diagnostic plots were shown in Figure 2. Figure 2A, 2B, 2C and 2D were used to assess the final models of metformin on BMI in patients with obesity, patients with type 1 diabetes mellitus, patients with nonalcoholic fatty liver, patients with precocity, respectively. As we could see, there were good linear relationships between individual predictions and observations, meaning the good fitting of the final models.

The visual predictive check plots were shown in Figure 3. Figure 3A, 3B, 3C and 3D, were used to evaluate the predictive performance of final models from metformin on BMI in patients with obesity, patients with type 1 diabetes mellitus, patients with nonalcoholic fatty liver, patients with precocity, respectively, in which most observed data were included in the 95% prediction intervals produced by simulation data, showing the predictive power of the final models.

3.4 Prediction

The trends of efficacy of metformin on BMI in patients with obesity, patients with type 1 diabetes mellitus, patients with nonalcoholic fatty liver, patients with precocity were shown in Figure 4A, 4B, 4C and 4D, respectively. In patients with obesity, the efficacy of metformin on BMI at 5.1 weeks was 25% of the E_{max}, at 15.2 weeks was 50% of the E_{max}, at 45.6 weeks was 75% of the E_{max}, at 60.8 weeks was 80% of the E_{max}. In patients with type 1 diabetes mellitus, the efficacy of metformin on BMI at 8.4 weeks was 25% of the E_{max}, at 25.2 weeks was 50% of the E_{max}, at 75.6 weeks was 75% of the E_{max}, at 100.8 weeks was 80% of the E_{max}. In patients with nonalcoholic fatty liver, the efficacy of metformin on BMI at 2.19 weeks was 25% of

the E_{max}, at 6.57 weeks was 50% of the E_{max}, at 19.71 weeks was 75% of the E_{max}, at 26.28 weeks was 80% of the E_{max}. In patients with precocity, the efficacy of metformin on BMI at 4.2 weeks was 25% of the E_{max}, at 12.4 weeks was 50% of the E_{max}, at 37.2 weeks was 75% of the E_{max}, at 49.6 weeks was 80% of the E_{max}.

4 Disscusion

Metformin was increasingly used to control weight in children and adolescents, such as patients with obesity(Atabek and Pirgon, 2008; Burgert et al., 2008; Love-Osborne et al., 2008; Clarson et al., 2009; Wilson et al., 2010; Yanovski et al., 2011; Gomez-Diaz et al., 2012; Kendall et al., 2013; van der Aa et al., 2016; Garibay-Nieto et al., 2017; Pastor-Villaescusa et al., 2017), patients with type 1 diabetes mellitus(Codner et al., 2013; Nadeau et al., 2015; Nwosu et al., 2015), patients with nonalcoholic fatty liver(Nadeau et al., 2009; Lavine et al., 2011), patients with precocity(Ibanez et al., 2006a; Ibanez et al., 2006b). However, lacking dosage and duration of treatment recommendation made it difficult to promote metformin usage in children and adolescents with different disease types for control of weight. The present study was to analyze the time course and dose effect from metformin on BMI using MBMA method and to recommend dosage and duration of treatment from metformin in children and adolescents with different disease types.

In the present study, the E_{max} of metformin on BMI in patients with obesity, patients with type 1 diabetes mellitus, patients with nonalcoholic fatty liver, patients with precocity were -10%, -4.31%, -4.7%, and -9.41%, respectively. The ET_{50} of metformin on BMI in patients with obesity, patients with type 1 diabetes mellitus, patients with nonalcoholic fatty liver, patients with precocity were 15.2 weeks, 25.2 weeks, 6.57 weeks, and 12.4 weeks, respectively. Of course, the present study was not isolated. In the previous study from Chen *et al*, the change rate of weight from baseline was selected as the efficacy indicator, and the ET_{50} in patients with obesity was 15.1 weeks(Chen et al., 2020b), which had the similar ET_{50} value with the present study. However, the population in the previous study was not entirely children and adolescents, and the number of previously included studies in Chen *et al*(Chen et al., 2020b) was also lower than that of the current study.

In addition, in our present study, no covariate (in particular metformin dosage) was incorporated into the E_{max} models, showing there was no significant dose dependence from metformin efficacy on BMI in children and adolescents with different disease types from the current included studies. In other words, we could recommend the lower limits of the metformin dose ranges on the basis of the current included studies for different disease types. Further, to achieve the 80% efficacy of E_{max}, which was called plateau, metformin treatment duration were 60.8 weeks, 100.8 weeks, 26.28 weeks and 49.6 weeks in patients with obesity, patients with type 1 diabetes mellitus, patients with nonalcoholic fatty liver, and patients with precocity, respectively. For type 1 diabetes mellitus, no study went beyond 9 months, yet

estimates for metformin effect were being extrapolated to 100.8 weeks, which would be further verified in the future research. Furthermore, countries were also analyzed in this study as a categorical covariable, however, were not included in the E_{max} models, revealing there was no significant country dependence from metformin efficacy on BMI in children and adolescents with different disease types from the current included studies.

The present study recommended that for patients with obesity, 1000 mg/day metformin was required for at least 15.2 weeks, and 60.8 weeks to achieve the plateau of metformin effect. However, in the study from Pu *et al*, effects of metformin in obesity treatment, they found high dose metformin (>1500 mg/d) was more effective in reducing BMI, yet more than half of their studies were on adults(Pu et al., 2020). In our study, only children and adolescents were involved. That was to say, the composition of the population would have a certain impact on the choice of dosage. The optimal dose for children and adolescents was lower than that for adults. In addition, for patients with type 1 diabetes mellitus, 1000 mg/day metformin was required for at least 25.2 weeks, and 100.8 weeks to achieve the plateau of metformin effect. For patients with nonalcoholic fatty liver, 1000 mg/day metformin was required for at least 6.57 weeks, and 26.28 weeks to achieve the plateau of metformin effect. For patients with precocity, 425 mg/day metformin was required for at least 12.4 weeks, and 49.6 weeks to achieve the plateau of metformin effect.

However, there were limited data for all the various dosages studied across the timeframe studied, for nonalcoholic fatty liver and precocity only 2 studies were identified. In addition, there were almost no studies on children younger than 4 years old included in the present study. In terms of geographical scope, the asian countries and populations involved in this study were small. Therefore, the results of this study would be further verified in the following clinical studies or trials.

5 Conclusion
It was the first time to analyze the time course and dose effect from metformin on BMI in children and adolescents and meanwhile to recommend dosage and duration of treatment for metformin in patients with obesity, patients with type 1 diabetes mellitus, patients with nonalcoholic fatty liver, patients with precocity, respectively. The recommendations would be validated in future clinical studies or trials.

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Table 1. Studies identified for analysis

Diseases	Studies	Countries	Groups	Dosages (g/day)	Duration of treatment	Body Mass Index (kg/m^2)	Number of people	Age (years)
Obesity	Pastor-Villaescusa (2017)	Spain	Metformin (Prepubertal)	1	6 months	28.2	40	6.8-15.3
			Placebo (Prepubertal)		6 months	29.2	40	6.8-15.3
			Metformin (Pubertal)	1	6 months	29.4	40	6.8-15.3
			Placebo (Pubertal)		6 months	30.6	40	6.8-15.3
Obesity	Garibay-Nieto (2017)	Mexico	Metformin	1	4 months	28.54	14	11.43 ± 2.1
			Placebo		4 months	28.79	17	12.59 ± 2.62
Obesity	van der Aa (2016)	Netherlands	Metformin	2	18 months	29.8	23	12.6-15.3
			Placebo		18 months	30.5	19	11.3-14.0
Obesity	Kendall (2013)	UK	Metformin	1.5	6 months	37.1	74	13.68 ± 2.3
			Placebo		6 months	35.95	77	13.64 ± 2.2
Obesity	Gómez-Díaz (2012)	Mexico	Metformin	1.7	12 weeks	31.1	28	7.0-16.4
			Placebo		12 weeks	27.1	24	4.4-15.91
Obesity	Yanovski (2011)	USA	Metformin	2	12 months	34.2	53	10.1 ± 1.6
			Placebo		12 months	34.6	47	10.4 ± 1.4
Obesity	Wilson (2010)	USA	Metformin	2	52 weeks	35.9	39	14.8 ± 1.3
			Placebo		52 weeks	35.9	38	15.0 ± 1.5
Obesity	Clarson (2009)	Canada	Metformin	1.5	6 months	36.4	11	10.1-16.1
			Placebo		6 months	33.9	14	10.1-16.1

Obesity	Burgert (2008)	USA	Metformin	1.5	4 months	41	15	15 ± 2
			Placebo		4 months	40	13	15 ± 1
Obesity	Atabek (2008)	Turkey	Metformin	1	6 months	28.5	90	11.83 ± 2.8
			Placebo		6 months	28	30	11.6 ± 2.7
Obesity	Love-Osborne (2008)	USA	Metformin	1.7	6 months	39.4	60	15.5 ± 1.7
			Placebo		6 months	39.3	25	14.2 ± 4.6
Type 1 diabetes mellitus	Nwosu (2015)	USA	Metformin	1	9 months	28	15	15.0 ± 2.5
			Placebo		9 months	27.7	13	14.5 ± 3.1
Type 1 diabetes mellitus	Nadeau (2015)	USA	Metformin	1	6 months	23.5	40	15.9 ± 1.7
			Placebo		6 months	24.3	40	16.0 ± 1.6
Type 1 diabetes mellitus	Codner (2013)	Chile	Metformin	1.7	9 months	23.7	13	17.7 ± 1.6
			Placebo		9 months	26.2	11	16.7 ± 1.7
Nonalcoholic fatty liver	Lavine (2011)	USA	Metformin	1	96 weeks	34	57	13.1 ± 2.4
			Placebo		96 weeks	33	58	12.9 ± 2.6
Nonalcoholic fatty liver	Nadeau (2009)	USA	Metformin	1.7	6 months	39.6	37	12-18
			Placebo		6 months	40.2	13	12-18
Precocity	Ibáñez (2006a)	Spain	Metformin	0.425	24 months	18.7	19	7.9 ± 0.2
			Placebo		24 months	18.1	19	8.0 ± 0.2

Precocity	Ibáñez (2006b)	Spain	Metformin	0.85	36 months	21	10	9.0 ± 0.1
			Placebo		36 months	20.2	12	9.1 ± 0.1

Table 2. Parameter estimates of final models

Model	Parameter	Estimate	Model	Parameter	Estimate
(A)	E_{max}, %	-10	(B)	E_{max}, %	-4.31
	ET_{50}, week	15.2		ET_{50}, week	25.2
	ω_{Emax}	6.025		ω_{Emax}	1.995
	ω_{ET50}	-		ω_{ET50}	-
	ε	0.27		ε	2.296
(C)	E_{max}, %	-4.7	(D)	E_{max}, %	-9.41
	ET_{50}, week	6.57		ET_{50}, week	12.4
	ω_{Emax}	2.062		ω_{Emax}	0.742
	ω_{ET50}	-		ω_{ET50}	-
	ε	0.01		ε	0.01

(A) patients with obesity; (B) patients with type 1 diabetes mellitus; (C) patients with nonalcoholic fatty liver; (D) patients with precocity. E_{max}, the maximal effects; ET_{50}, the treatment duration to reach half of the the maximal effects; ω_{Emax}, inter-study variability of E_{max}; ω_{ET50}, inter-study variability of ET_{50}; ε, residual error.
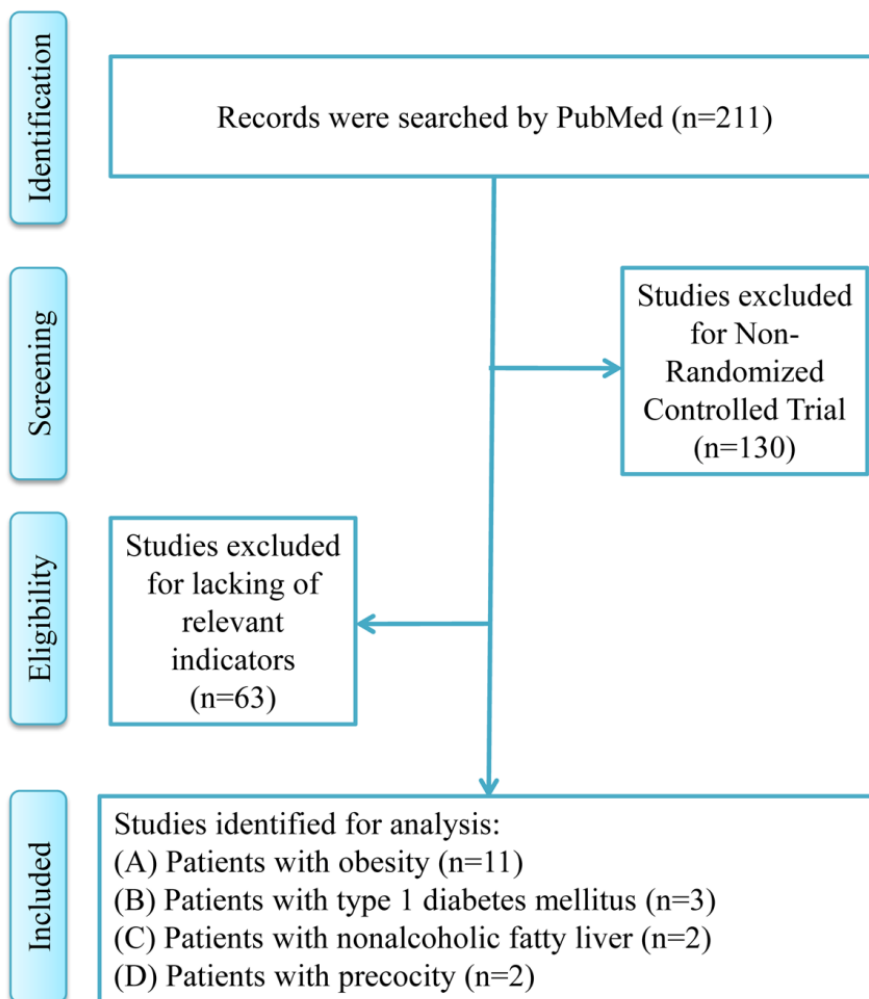
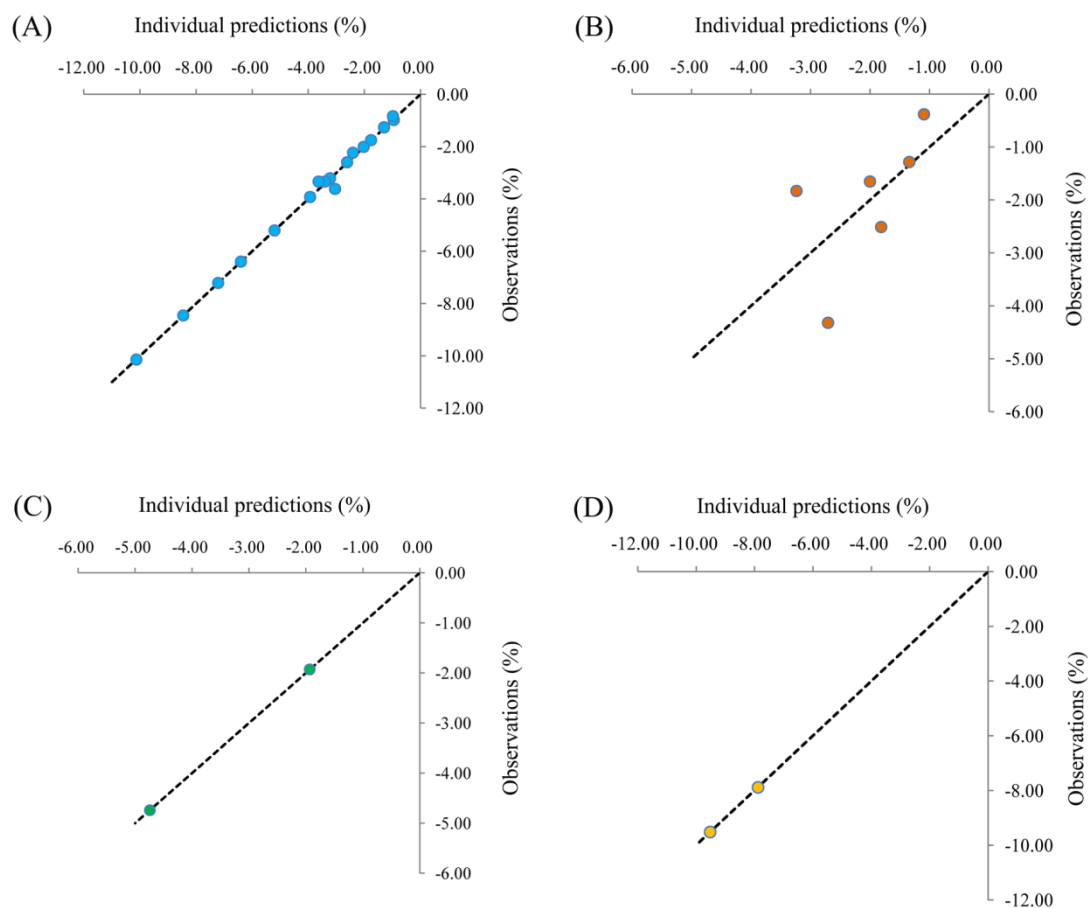**Figure 1. The strategy for Literature search.**

Figure 2. Visual inspection of routine diagnostic plots.
(A) patients with obesity, (B) patients with type 1 diabetes mellitus, (C) patients with nonalcoholic fatty liver, (D) patients with precocity.
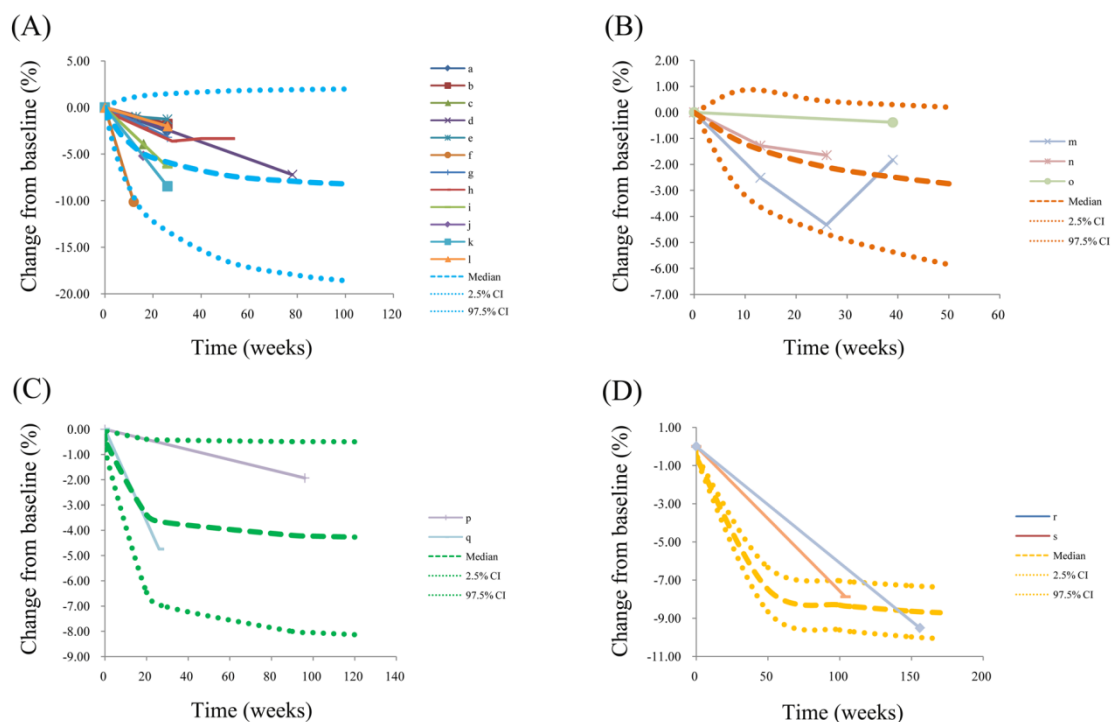
Figure 3. Prediction-corrected visual predictive check plots

(A) patients with obesity, (B) patients with type 1 diabetes mellitus, (C) patients with nonalcoholic fatty liver, (D) patients with precocity. Median, 2.5% CI and 97.5% CI were simulated by Monte Carlo (n=1000); CI, confidence interval; a, Pastor-Villaescusa (2017)(Pastor-Villaescusa et al., 2017); b, Pastor-Villaescusa (2017)(Pastor-Villaescusa et al., 2017); c, Garibay-Nieto (2017)(Garibay-Nieto et al., 2017); d, van der Aa (2016)(van der Aa et al., 2016); e, Kendall (2013)(Kendall et al., 2013); f, Gómez-Díaz (2012)(Gomez-Diaz et al., 2012); g, Yanovski (2011)(Yanovski et al., 2011); h, Wilson (2010)(Wilson et al., 2010); i, Clarson (2009)(Clarson et al., 2009); j, Burgert (2008)(Burgert et al., 2008); k, Atabek (2008)(Atabek and Pirgon, 2008); l, Love-Osborne (2008)(Love-Osborne et al., 2008); m, Nwosu (2015)(Nwosu et al., 2015); n, Nadeau (2015)(Nadeau et al., 2015); o, Codner (2013)(Codner et al., 2013); p, Lavine (2011)(Lavine et al., 2011); q, Nadeau (2009)(Nadeau et al., 2009); r, Ibáñez (2006)(Ibanez et al., 2006a); s, Ibáñez (2006)(Ibanez et al., 2006b).
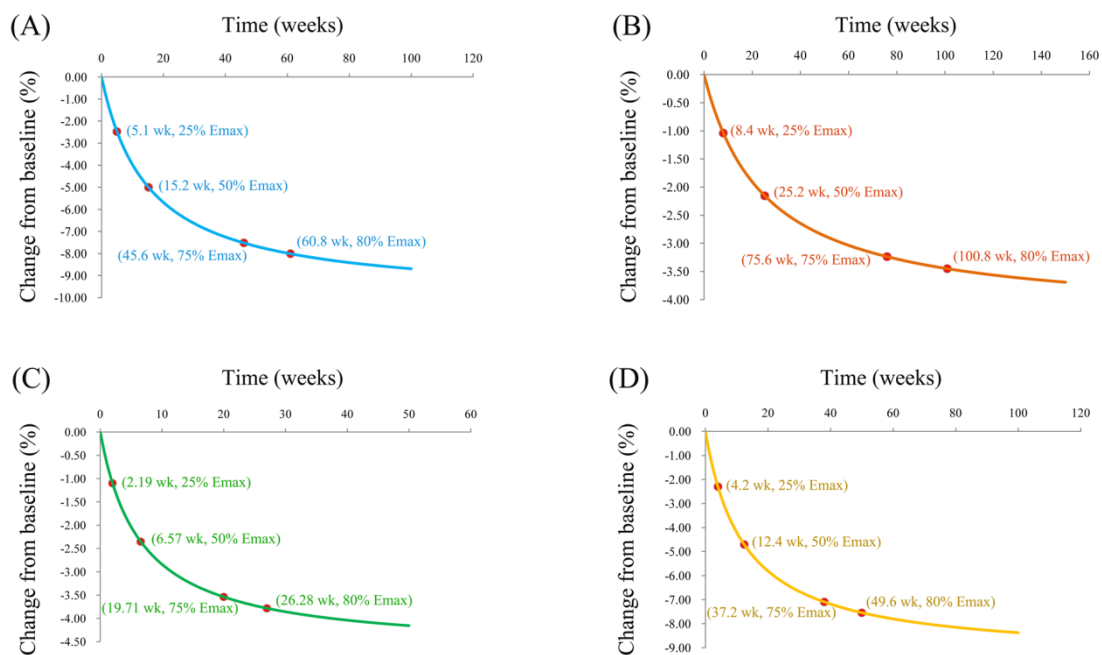
Figure 4. Model prediction.
(A) patients with obesity, (B) patients with type 1 diabetes mellitus, (C) patients with nonalcoholic fatty liver, (D) patients with precocity.