



Background and Objectives

Very low calorie diets (VLCD) are commonly used to loose weight (WT) quickly but for patients with type 2 diabetes (T2DM), the diet will also decrease the fasting plasma glucose (FPG). There are two hypothesis for the causal link between the dieting and the reduction of FPG: 1) the WT loss resulting from the diet will increase the insulin sensitivity (IS) which reduces FPG, and 2) the diet causes a change in the system that affects WT as well as insulin sensitivity and thus also FPG. The underlying change of the system for hypothesis 2) has been suggested to be the concentration of free fatty acids (FFA), which is known to affect IS [2]. The aim of this study was to implement and test these hypotheses using non-linear mixed effects modelling on summary level data from publications of weight loss and FPG with VLCD.

Methods and Materials

Summary level data was gathered from 8 clinical studies of diabetic patients treated with VLCD where WT as well as FPG was measured [3-10]. There were in total 13 arms in the all studies; all with varying number of subjects per arm (median = 8; range = 6-62), baseline WT (median = 106 kg; range = 93-118 kg), baseline FPG (median = 253 mg/dL; range = 91-321 mg/dL) and (median = 8.9 yrs; range = 0.8-13.3 yrs). The subjects in the studies were treated with diets ranging from 330 to 909 kcal/day for a period of up to 224 days. Measurements of WT and FPG were taken regularly throughout the course of the studies.

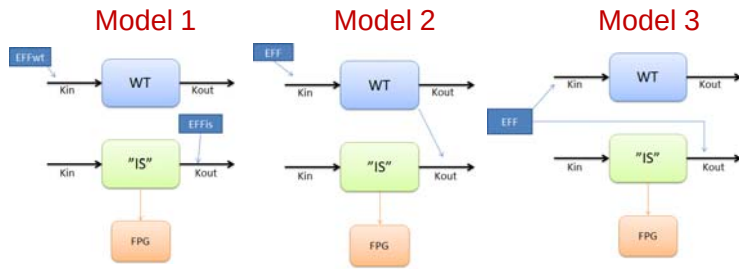


Figure 1. The hypothesised models that describe the effect of very low calorie diet (VLCD) on weight and FPG. Left: Model 1, the reference model whereby weight and FPG is totally unrelated. Middle: Model 2, which describes an inhibitory effect on weight input, which leads to weight change (dWT) inhibiting mediator ("IS") output, resulting in decreased FPG. Right: Model 3, which describes an underlying mechanism that inhibits both weight input and mediator output.

Both WT and IS were modelled using indirect response models. For hypothesis 1, the diet was implemented as an instantaneous inhibitory effect on the input of the WT model. The change in WT was then implemented as an inhibitory effect on the output of IS (Model 2). For hypothesis 2, the diet was implemented as a instantaneous effect inhibiting both the WT input and the IS output (Model 3). Potential non-linearity of the effect of WT on IS was tested using a power and Emax function. A model allowing the effects of diet to be completely independent on WT and IS is the most flexible model and was thus explored for comparison reasons (Model 1). The effect of IS on FPG is in all models implemented as a direct effect ensuring that a healthy FPG (FPG=72 mg/dL) translates to an IS=1, using the relationship in equation (Eq. 1). To account for the difference in the size between the study arms from which the data was extracted the residual error was divided by the square root of the number of patients in that arms. Once the best structural model of model 2 and 3 was determined, the presence of study covariate effects was investigated using the stepwise covariate model building as implemented in PsN. Tested covariates were: baseline BMI, diet size, age, and disease duration. Non-linear mixed-effects modelling was performed using NONMEM 7.2 with the FOCEI method.

$$IS_{baseline} = 72/FPG_{baseline}$$

$$IS_{logit} = \ln(IS_{baseline}/(1 - IS_{baseline}))$$

$$k_{in,IS} = k_{out,IS} \cdot IS_{logit}$$

$$dIS_{logit}/dt = k_{in,IS} - k_{out,IS} \cdot IS_{logit}$$

$$IS = e^{IS_{logit}} / (1 + e^{IS_{logit}})$$

$$FPG = 72/IS$$

Eq. 1

Results

When evaluating all 3 models in terms of objective function value (OFV), model 1 had, as expected, the lowest OFV. Model 3 had 17 higher OFV points than model 1, but 100 OFV points lower than model 2, suggesting that hypothesis 2 for these data is more accurate.

There were no evidence for the existence of a non-linearity effect in the models, as the tested power and Emax functions collapsed back into their respective linear forms (results not shown).

Two covariate relationships were found to be significant and physiological plausible: diet size effect on Kout WT, and baseline BMI on Kout of IS. The inclusion of the aforementioned covariates further reduced 78 OFV units of the model (Table 1).

Table 1. The final estimates of the structural models and their inter-individual variability (CV%). Model 1 had no relationships between WT and IS, and its estimates and OFV are for reference only. Model 3 with an underlying mechanism affecting both WT and IS was found to be a better model than Model 2, which has the change of WT affecting IS. Diet on Kout of WT and Baseline BMI on Kout of IS were significant covariates that further improved the model fit.

Parameter	Model (CV %)	Model 1	Model 2*	Model 3
Baseline WT (kg)		104 (6.80)	104 (7.14)	104 (6.78)
Baseline FPG (mg/dL)		243 (16.9)	210 (23.7)	242 (20.3)
Kout, WT (/day)		0.0149	0.0105	0.0147
Kout, IS (/day)		0.334	0.0263	0.216
EFF, WT		0.674 (24.0)	0.683 (14.8)	-
EFF, IS		0.857 (85.6)	-	0.683 (15.5)
Covariate, Diet on Kout WT		-6.73	-	-6.98
Covariate, Baseline BMI on Kout IS		0.267	-	0.162
Residual error, WT		0.0113	0.019	0.0112
Residual error, FPG		0.381	0.963	0.488
OFV (no covariates)		801	918	818
OFV (with covariates)		716	-	740

*The parameters for Model 2 were estimated without covariates.

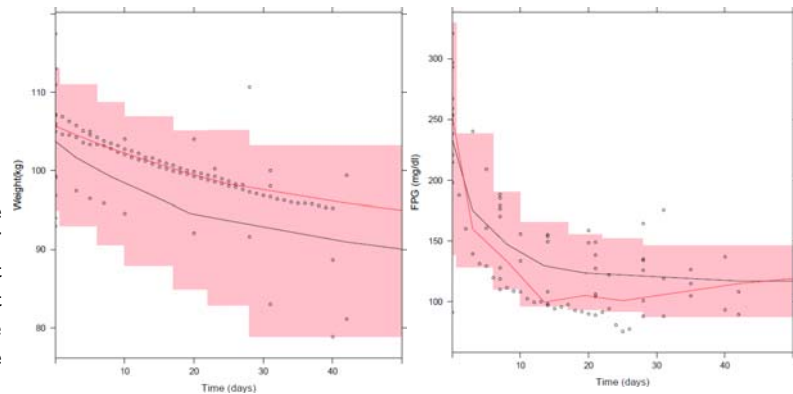


Figure 2. Visual Predictive Check (VPC) for the final model (Model 3). Black circles indicate observations from the study arms; Black line indicate the median of the observations; Red shaded area indicate the 80% prediction interval of 1000 simulated datasets from the model; Red line indicate the median line of the predictions. Left: VPC for weight (kg). Right: VPC for FPG (mg/dL).

Conclusions

- The model with an underlying mechanism that affects both weight and IS was found to better describe the data than using weight loss as driving the change in IS.
- Diet size and baseline BMI were significant covariates acting on the Kout of WT and Kout of IS, respectively.

References

- [1] Henry RR, et al. (1986) *Diabetes* 35 (9):990-998
- [2] Guillaume-Gentil C, et al. (1993) *Diabetologia* 36 (10):899-906
- [3] Nagulesparan M, et al. (1981) *Journal of Clinical Endocrinology and Metabolism* 53 (3):560-568
- [4] Hughes TA, et al. (1984) *The American Journal of Medicine* 77 (1):7-17
- [5] Henry RR, et al. (1985) *Journal of Clinical Endocrinology and Metabolism* 61 (5):917-925
- [6] Amatruda JM, et al. (1988) *Archives of Internal Medicine* 148 (4):873-877
- [7] Bauman WA, et al. (1988) *The American Journal of Medicine* 85 (C):38-46
- [8] Gumbiner B, et al. (1996) *American Journal of Clinical Nutrition* 63 (1):110-115
- [9] Gougeon R, et al. (1997) *American Journal of Clinical Nutrition* 65 (3):861-870
- [10] Christiansen MP, et al. (2000) *Diabetes* 49 (10):1691-1699