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Insulin resistance in obese patients with type 2 diabetes mellitus : effects of a very low calorie diet

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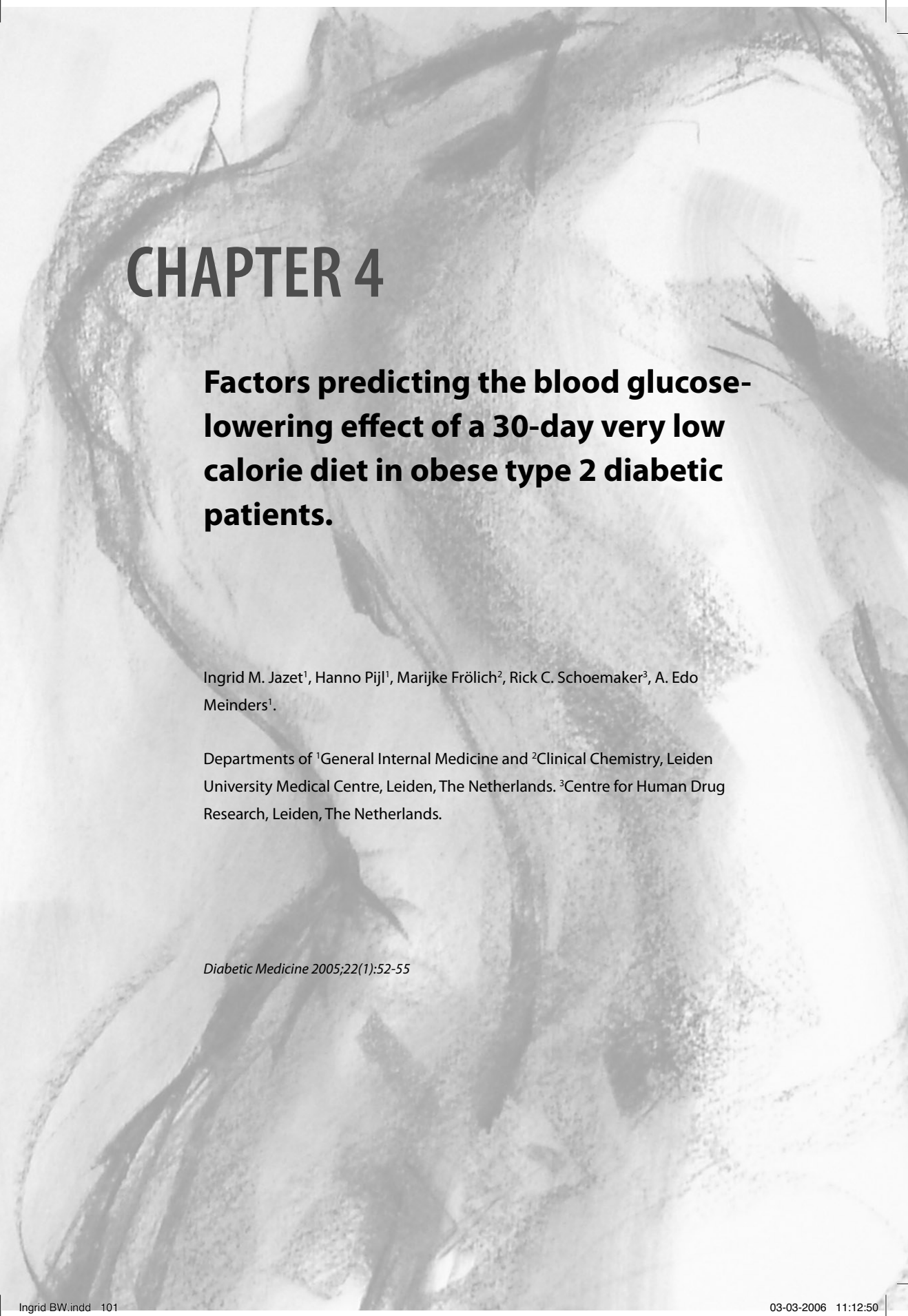
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CHAPTER 4

Factors predicting the blood glucose-lowering effect of a 30-day very low calorie diet in obese type 2 diabetic patients.

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ABSTRACT

Calorie restriction and weight loss improve hyperglycaemia in some but not all obese patients with type 2 diabetes mellitus. To identify specific endocrine and metabolic markers that predict a favourable response to a very low calorie diet (VLCD), 17 obese (BMI 37.6 ± 5.6 kg/m² [mean $\pm$ SD]) type 2 diabetic (FPG 12.9 ± 3.1 mmol/L, HbA_{1c} $8.6 \pm 1.6\%$) patients were studied on day 0, 2, 10 and 30, of a VLCD (Modifast®, 450 kCal/day). A responder was a priori defined as a patient with a fasting plasma glucose concentration (FPG) < 10 mmol/L on day 30. All blood glucose-lowering medication (including insulin) was discontinued on day -1. On day 2 and 30 of the VLCD an intravenous glucose tolerance test (IVGTT) was performed.

Of the 14 patients who completed the 30-day VLCD, eight qualified as responder. Responders and non-responders could be distinguished by day 2. Responders had a shorter duration of type 2 diabetes and higher fasting serum insulin, C-peptide and HOMA- β -values. In addition, responders displayed a more prominent second-phase insulin response following i.v. glucose loading and higher k-values. In a stepwise discriminant analysis, the change in FPG from day 0 to day 2 (responders $+ 0.64 \pm 2.3$, non-responders $+ 4.15 \pm 3.3$ mmol/L, $p = 0.035$) in combination with the area under the curve of insulin (AUC) above baseline during an IVGTT on day 2 (responders 571 ± 236 , non-responders 88 ± 65 mU*50min, $p < 0.001$), distinguished responders completely from non-responders.

In conclusion, preservation of the capacity of β -cells to secrete insulin predicts a favourable metabolic response to a VLCD in obese type 2 diabetic patients. Already on day 2 a decline in FPG levels can be found in those patients that react favourably to the diet. Nevertheless, even in patients who qualified as non-responders, no gross hyperglycaemia (> 20 mmol/L) or any other side effects were observed.

INTRODUCTION

Over 80% of type 2 diabetic patients are obese¹. Numerous studies have shown that calorie restriction and weight loss can reverse their metabolic abnormalities²⁻¹⁰. After initiation of a very low calorie diet (VLCD), hyperglycaemia decreases within 4-10 days, even before significant weight loss has occurred^{4,5,8}. In one study, a decrease in fasting plasma glucose (FPG) was detected within 2 days¹¹. Another⁴ study reported patients who failed to respond but an explanation was not given.

Neither the mechanism nor the factors that predict the blood glucose-lowering effect of energy restriction and weight loss have been established. The current study was undertaken to determine (i) if a decrease in FPG would occur within 2 days after the initiation of a VLCD and (ii) which factors predict a favourable metabolic response (defined as a FPG < 10 mmol/L on day 30) during a prolonged VLCD in obese type 2 diabetic patients when all blood glucose-lowering medication is discontinued.

PATIENTS AND METHODS

In 17 obese (BMI 37.6 ± 5.6 kg/m², mean $\pm$ SD) type 2 diabetic patients (duration 8.0 ± 5.8 years) who had persistent high blood glucose levels (12.9 ± 3.1 mmol/L) and HbA_{1c} percentages ($8.6 \pm 1.6\%$) despite maximal doses of oral blood glucose-lowering medication and/or insulin (66-340 units/day), all blood glucose-lowering medication was stopped (day -1) and a very low calorie diet (Modifast®, Novartis Consumer Health, Breda, the Netherlands, 450 kCal/day) was started for 30 days.

On days 0, 2, 10 and 30, body weight was measured, and fasting glucose, insulin, C-peptide and leptin were determined. In addition, an intravenous glucose tolerance test (IVGTT, 25 g of glucose i.v. in 4 min with blood sampling at 0, 2, 4, 6, 8, 10, 12, 20, 30, 40, 50 and 60 min) was performed after an overnight fast at days 2 and 30 of the VLCD^{12,13}. We chose day 2 instead of day 0 for the first IVGTT because most patients had used NPH insulin the evening before the start of the study. For the same reason we used laboratory measures taken on day 2 for baseline values of fasting plasma insulin and C-peptide.

Statistical analysis and mathematical calculations

Values are presented as mean $\pm$ standard deviation (SD).

The glucose disappearance rate (k-value) was determined by (natural) log-linear regression of the glucose concentrations against time over the period from 10 to 60 min post-glucose loading¹². The area under the curve (AUC) of glucose and of insulin were determined over the period from 0 to 60, respectively 10 to 60 min post-glucose loading from zero level using the linear trapezoidal rule. The AUC of glucose and insulin above baseline were also calculated. Baseline was defined as plasma glucose and insulin levels at time 0 min.

Table 1. Metabolic response to a VLCD in responders and non-responders.

	Responders (n=8)			Non-responders (n=6)		
	Day 0	Day 30	P	Day 0	Day 30	P
FPG (mmol/L)	12.3 ± 2.3	7.9 ± 1.2 [†]	0.001	13.4 ± 3.8	17.3 ± 4.4 [†]	NS
Leptin (mg/mL)	31.7 ± 24.7	12.4 ± 8.9	NS	22.2 ± 8.3	8.2 ± 3.1	0.003
Body weight (kg)	119.4 ± 21.2	107.2 ± 20.3	0.0001	101.9 ± 6.9	89.7 ± 6.8	0.0001
BMI (kg/m ²)	39.3 ± 7.1	35.3 ± 6.7	0.0001	37.1 ± 3.6	32.7 ± 3.4	0.0001
	Day 2	Day 30	P	Day 2	Day 30	P
FI (mU/L)	30.6 ± 16.0 [†]	18.8 ± 9.9 [†]	0.034	12.8 ± 5.0 [†]	8.3 ± 2.0 [†]	NS
FCP (nmol/L)	1.8 ± 0.7 [†]	1.1 ± 0.4	0.003	0.8 ± 0.1 [†]	0.6 ± 0.2	0.042
AUC of insulin (mU*50 min)	2014 ± 978 [†]	1494 ± 906 [†]	0.042	775 ± 201 [†]	388 ± 115 [†]	0.040
AUC of insulin above baseline (mU*50 min)	571 ± 236 [†]	552 ± 425 [†]	NS	88 ± 65 [†]	66 ± 73 [†]	NS
AUC of glucose (mmol*60 min)	1094 ± 132 [†]	860 ± 81 [†]	0.0001	1355 ± 274 [†]	1305 ± 240 [†]	NS
AUC of glucose above baseline (mmol*60 min)	344 ± 107	372 ± 40 [†]	NS	372 ± 32	280 ± 78 [†]	NS
k-Value (%/min)	0.51 ± 0.08 [†]	0.55 ± 0.08 [†]	NS	0.37 ± 0.13 [†]	0.36 ± 0.12 [†]	NS
HOMA-IR	17.4 ± 9.2	6.7 ± 3.9	0.004	9.3 ± 2.7	6.5 ± 2.6	NS
HOMA-β	69.9 ± 42.4 [†]	86.8 ± 44.8 [†]	NS	22.2 ± 15.6 [†]	13.1 ± 5.4 [†]	NS

Data are presented as mean ± standard deviation. FI: fasting serum insulin; FCP: fasting serum C-peptide.

* P < 0.0001; † P < 0.05; ‡ P < 0.001, all responders *versus* non-responders

Estimates of insulin resistance and β-cell function by HOMA score were calculated with the formulas as described by Matthews *et al.*¹⁴.

Comparisons between groups (i.e., responders *versus* non-responders) were made with the Student's *t*-test for independent samples. Within groups comparisons were made with the Student's *t*-test for paired samples. Stepwise discriminant analysis was performed to determine prognostic factors for distinction between responders and non-responders. *A priori*, a responder was defined as a patient with a FPG < 10 mmol/L on day 30.

A p-value of < 0.05 was considered statistically significant.

RESULTS

Fourteen out of the 17 patients completed the 30-day VLCD.

By 2 days of a VLCD, when weight loss was still minimal (responders -2.8 ± 0.7 kg, non-responders -2.4 ± 0.7 kg, NS), a distinction between responders and non-responders could be made. Responders showed only a minimal rise or even a decrease in FPG at day 2 (+0.64 ± 2.3 mmol/L), whereas non-responders had an increase in FPG (+4.15 ± 3.3 mmol/L), p = 0.035. On day 10, FPG had improved in responders (-2.7 ± 2.9 mmol/L) and remained more or less

the same in non-responders ($+4.2 \pm 5.5$), $p = 0.011$. After 30 days, FPG improved further in responders (-4.3 ± 2.4 mmol/L) whereas FPG remained elevated in non-responders ($+3.9 \pm 5.2$ mmol/L), $p = 0.002$. All values given are compared with day 0 (Table 1).

Responders had a significantly higher fasting serum insulin and C-peptide concentration and HOMA- β on day 2 compared with non-responders (Table 1). During an IVGTT, responders had a significantly higher AUC and AUC above baseline of insulin (second-phase insulin response) on day 2 than non-responders. A first-phase insulin response was lacking in both groups on day 2 and day 30 (Fig. 1).

Neither the initial weight and fat mass nor the extent of weight loss (-12.2 ± 3.6 kg in responders, -12.2 ± 2.5 kg in non-responders, NS), or the decline in serum leptin were different between responders and non-responders. Previous blood glucose-lowering therapy and initial FPG were also similar in responders and non-responders.

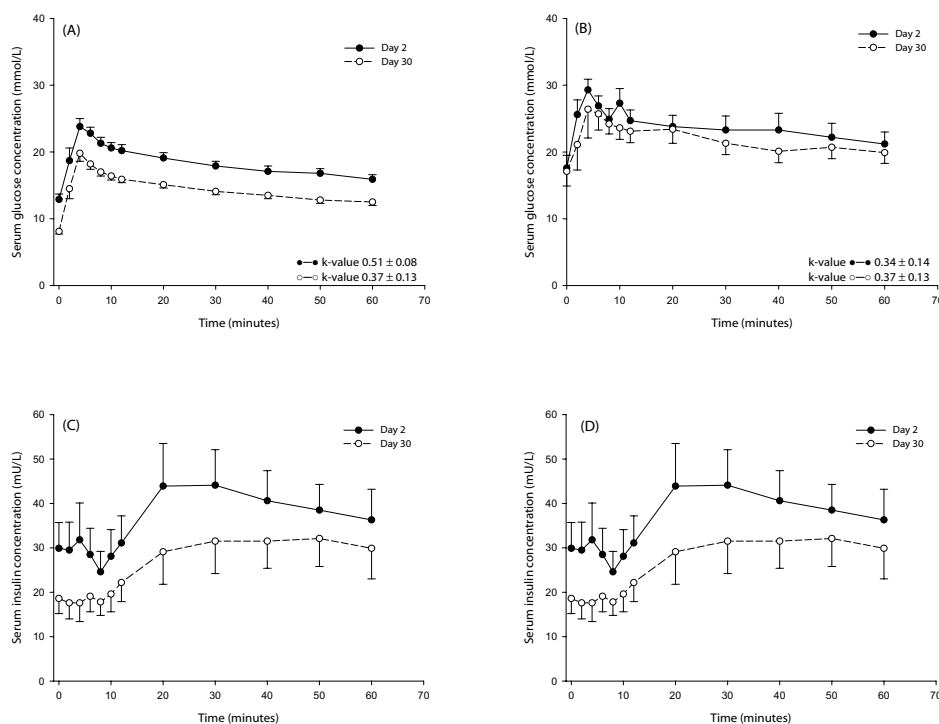


Figure 1.

Glucose excursions (top, A, B) and insulin secretion (bottom, C, D) of responders (left, A, C) and non-responders (right, B, D) after an intravenous glucose load on day 2 (closed circles) and day 30 (open circles) of a VLCD. Responders have a lower area under the curve (AUC) of glucose, a higher AUC of insulin and a higher k-value. After a 30-day VLCD, fasting plasma glucose (FPG) and fasting serum insulin decrease but incremental AUC of glucose and insulin do not change and neither do the k-values. Note that both responders and non-responders lack a first-phase insulin response. Data are presented as mean $\pm$ SEM.

Stepwise discriminant analysis was performed to determine prognostic factors for distinction between responders and non-responders. The change in FPG from day 0 to day 2 combined with the AUC of insulin above baseline during an IVGTT on day 2 completely separated responders from non-responders. When IVGTT data were left out of the analysis, fasting C-peptide on day 2 and duration of diabetes were identified as discriminating factors although in this analysis two responders were misclassified as non-responders.

DISCUSSION

We examined the effect of a 30-day VLCD on FPG levels and glucose handling after an intravenous glucose load in obese type 2 diabetic patients in whom all blood glucose-lowering medication was discontinued. *A priori*, responders were defined as those patients who would have a FPG level less than 10 mmol/L on day 30.

It was found that within 2 days of a VLCD, when weight loss was still minimal (reflecting salt and fluid loss), a distinction between responders and non-responders could be made. Responders exhibited only a minimal increase or even a decrease in FPG at day 2 whereas non-responders showed a considerable increase in FPG.

Preservation of β -cell function appeared to predict a favourable response to a VLCD. Thus, responders had higher fasting serum insulin and C-peptide levels and a higher HOMA- β than non-responders on day 2. In addition, responders had a higher second-phase insulin response during an IVGTT. Other factors associated with a favourable response were a shorter duration of type 2 diabetes mellitus and higher k-values. Weight loss and the fall of serum leptin concentrations were not discriminating. A stepwise discriminant analysis showed that change in FPG from day 0 to day 2 combined with the AUC of insulin above baseline during an IVGTT on day 2 could fully discriminate responders from non-responders.

The fact that FPG improved by 2 days of a VLCD confirms earlier observations^{2,4-6,8} that reduced caloric intake and not weight loss is of prime importance to the early blood glucose reduction. The mechanism of this early beneficial effect on glucose metabolism is unclear although several studies have reported a close association of FPG with hepatic glucose output (HGO)^{3-5,7,8,15}.

After 30 days of a VLCD, both responders and non-responders had lost about 12 kg of body weight. Both groups had a decrease in fasting serum insulin but it remained significantly higher in responders than in non-responders. HOMA- β was also higher in responders compared with non-responders and did not change significantly in either group after a 30-day VLCD. HOMA-IR was similar in both groups after 30 days of a VLCD.

In a dynamic test (IVGTT), AUC of glucose above baseline, k-values and the amount of insulin secreted remained the same after 30 days of a VLCD in both responders and non-responders. Thus, the only factors that changed favourably after 30 days of a VLCD were a lower FPG in

responders and lower fasting serum insulin concentrations in both groups. This lower FPG in responders, in the presence of a lower serum insulin concentration, might have been caused by an increased sensitivity of the liver for insulin suppression of HGO. Because the k-values did not improve, we have no arguments for an increased peripheral glucose disposal.

This study again stresses the potential of diet therapy in obese type 2 diabetic patients. Eight out of the 14 (57%) patients had a decrease in FPG levels and none of those eight had to be restarted on insulin during a weight-maintaining diet (data not shown). We are aware, however, that our study included small numbers and follow-up was limited.

In conclusion, this study shows that by 2 days of a VLCD a distinction can be made between those who will react favourably to the diet and those who will not. Responders can be identified on the basis of a preserved capacity of the β -cell to secrete insulin. In this study, the change of the fasting plasma glucose concentration during the first 2 days of the VLCD in combination with the AUC of insulin above baseline during an IVGTT on day 2 could separate responders completely from non-responders.

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