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**RESEARCH ARTICLE**

# Pancreatin therapy in patients with insulin-treated diabetes mellitus and exocrine pancreatic insufficiency according to low fecal elastase 1 concentrations. Results of a prospective multi-centre trial

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## Abstract

**Background** Recently, high prevalence of exocrine dysfunction in diabetic populations has been reported. Patients with fecal elastase 1 concentration (FEC) <100 μg/g have also been demonstrated to suffer from steatorrhea in about 60% of cases, indicating the need of pancreatic enzyme replacement therapy. Until now, there have only been a few reports on the use of enzyme replacement therapy in diabetic patients with exocrine pancreatic insufficiency. This investigation was designed to evaluate the impact of enzyme-replacement therapy on glucose metabolism and diabetes treatment in a prospective study of insulin-treated patients with diabetes mellitus.

**Methods** A total of 546 patients with diabetes mellitus requiring insulin treatment were screened for exocrine dysfunction by FEC measurements. One hundred and fifteen patients (21.1%) had FEC <100 μg/g (normal >200 μg/g). Of these, 95 patients entered the study and 80 patients were randomized to receive either pancreatin (Creon®) (39 patients) or placebo (41 patients) in a double-blind manner. Parameters of glucose metabolism, diabetes therapy and clinical symptoms were recorded in standardized protocols for 16 weeks.

**Results** During the observation phase of 16 weeks, there were no significant differences between both groups concerning $HbA_{1c}$, fasting glucose levels, 2-h pp glucose levels, clinical parameters and safety parameters. A reduction in mild and moderate hypoglycemia was observed in the pancreatin group at the end of the study.

**Conclusions** Pancreatin therapy can be used safely in patients with diabetes mellitus and exocrine dysfunction. Parameters of glucose metabolism were not improved by enzyme replacement therapy. Copyright © 2006 John Wiley & Sons, Ltd.

**Keywords** type 1 diabetes mellitus; IDDM; exocrine pancreatic function; pancreatitis; fecal elastase 1 concentration; enzyme replacement therapy

# Introduction

Exocrine and endocrine pancreas are linked morphologically and functionally [1,2]. Changes in morphology and function of the exocrine pancreas in diabetes mellitus have been the subject of a number of publications over the last decades [3–15]. It can be summarised today that characteristics of exocrine pancreatic dysfunction are very frequent in both type 1 and type 2 diabetes mellitus as compared to that in healthy controls. Using fecal elastase 1 concentrations (FEC) as a marker of exocrine function, we found exocrine insufficiency to be present in about 35% of 697 patients with type 2 diabetes mellitus and about 50% of 323 type 1 patients [16]. Other recent studies reported very similar results [17,18]. Measuring fecal fat excretion in patients with diabetes mellitus and FEC $<100$ μg/g, steatorrhea was observed in about 60%, indicating relevant, severe damage of the exocrine function [19]. Steatorrhea indicates quantitative and qualitative fat maldigestion. It has been described to be associated with low vitamin D levels and osteoporosis [20] and it might also interfere with the regulation of glucose metabolism, since free fatty acids (FFA) have effects on beta cell function [19,21]. Although a significant proportion of diabetic patients seem to have a need for enzyme replacement therapy, very few reports are available on this topic. The results appear contradictory [22–24]. Therefore, a double-blind prospective study was designed to investigate the effects of enzyme replacement therapy on glucose metabolism and clinical symptoms in a group of insulin-treated diabetic (IDDM) patients with FEC $<100$ μg/g with an observation phase of 16 weeks.

# Subjects and methods

## Study design

The study is a randomised double-blind controlled trial. In a multi-centre setting (14 centres), patients with insulin treatment for diabetes mellitus were screened for FEC ($<100$ μg/g) after informed consent. Patients were randomised to receive either pancreatin (Creon®) or placebo in a double-blind manner. Study medication was taken three times a day with the main meals (4 capsules of 10 000 FIP units pancreatin or placebo). Additionally, two or three snacks accompanied by intake of two capsules of 10 000 FIP units of pancreatin or placebo were allowed. Clinical parameters were evaluated using a standard case report form including diabetes history (age at onset, duration, treatment, insulin dose, number of mild and severe hypoglycemia) and clinical symptomatology (number of stools, stool consistency (1 = hard − 4 = watery), flatulence (0 = none − 3 = severe), abdominal pain (0 = none − 3 = severe) and clinical global impression (assessed by investigator and patient). Clinical parameters and symptoms were assessed at weeks 0, 1, 2, 4, 10 and 16.

## Exclusion criteria

Patients with any severe diseases, any type of malignancy, any history of gastrointestinal surgery, any known reason for maldigestion or malabsorption, any history of alcohol or drug abuse, proven gastroparesis or diarrhea were excluded from the investigation.

*Laboratory methods*

FEC were determined by a commercially available ELISA test kit (Schebo Biotech, Giessen, Germany).

$HbA_{1c}$, fasting glucose, 1 and 2 h glucose were determined by standard procedures. To determine fat digestion, vitamin levels (A, D, E) were measured by standard procedures.

*Safety parameters*

Safety parameters included the report of adverse events, the evaluation of vital signs and physical examination as well as laboratory parameters including hematology, blood chemistry and urine analysis. The results were recorded in standard forms.

*Ethics*

The study design was approved by the Ethics committee of each centre. The study was done according to GCP.

*Statistics*

Statistical evaluation were done using the statistical software packages SPSS for windows 11.5.1 and SAS. $HbA_{1c}$ and fasting glucose were tested by a repeated measures analysis of covariance (GLM procedure) including the baseline values as covariates and treatment, visit and treatment by visit interactions as fixed factors. *P*-values $<0.05$ were considered as statistically significant. Secondary efficiency parameters were analysed descriptively by presenting summary statistics (e.g. mean, standard deviation).

# Results

A total of 546 patients with diabetes mellitus requiring insulin treatment were screened for exocrine dysfunction by FEC measurements. One hundred and fifteen patients (21.1%) had FEC $<100$ μg/g (half of the lower level of normal). Of these, 95 patients entered the study and 80 patients were randomized to receive either pancreatin (Creon®) or placebo. Forty-one patients were randomized to the placebo group (16 female, 25 male, mean age 43.2 years (23–63), mean BMI 25.3 kg/m$^2$ (18.3–31.2)) and 39 to the pancreatin group (13 female, 26 male, mean age 45.3 years (29–62), mean BMI 26.4 kg/m$^2$ (19.2–35.5)). Figure 1 shows the daily insulin doses reported at weeks 0 (before randomization), week 4 and



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week 16. The insulin doses did not change significantly during the observation period. $HbA_{1c}$ increased slightly in both groups (Figure 2), yet no significant difference between the groups could be observed. Two-hour glucose values following oral glucose load (75 g) did not change during the observation period and there were no important differences between both groups (Figure 3).

Clinical symptoms did not differ between groups nor change during the observation period to a significant degree (Table 1). While vitamin A levels remained unchanged in both groups, there was an increase in vitamin D levels in the pancreatin group and an increase in vitamin E levels in both groups during the observational period (data given in Table 2). The number of registered episodes of hyperglycemia and severe hypoglycemia did not differ significantly between the pancreatin and the placebo group throughout the 16 weeks. At the beginning of treatment, however, a baseline difference in the number of mild or moderate episodes of hypoglycemia was observed. There were more mild or moderate episodes of hypoglycemia in the pancreatin group. At week 16, both groups were equal ($p > 0.05$), therefore showing a reduction in mild and moderate hypoglycemia in the treatment group at week 16 (see Figure 4). Treatment-emergent adverse events occurred in 33 patients (84.6%) in the pancreatin group and in 35 (85.4%) in the control group. The most frequent adverse events were headache, infection, pain, diarrhea and dyspepsia. The evaluation of laboratory values, physical examinations and vital signs did not reveal any safety differences between both groups.

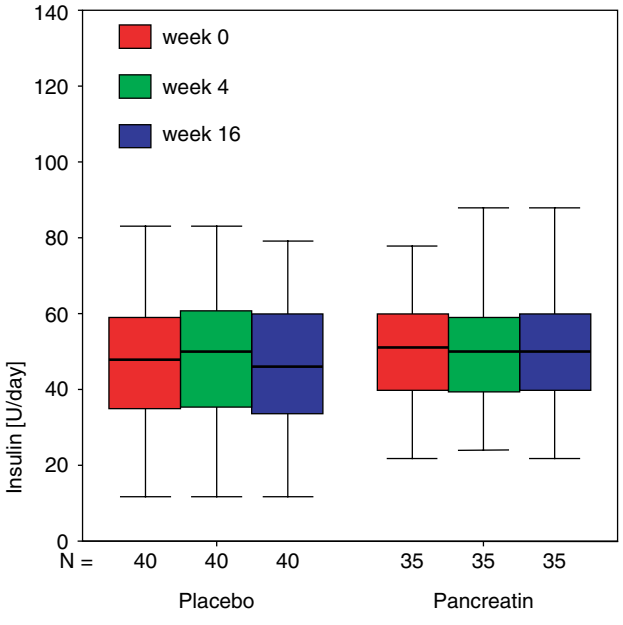


**Figure 1. Daily insulin doses reported at weeks 0, 4 and 16 during treatment with pancreatin or placebo**

## Conclusions

Pathological findings of exocrine function and exocrine morphology are frequent in both, type 1 and type 2 diabetes mellitus [3–18]. In diabetic patients with reduced FEC (an indirect marker of exocrine pancreatic function), about 60% have been reported to suffer from steatorrhea [19]. Although half of these patients with reduced FEC do not complain about significant gastrointestinal symptoms related to steatorrhea, they still might suffer from qualitative fat maldigestion, for example, lack of vitamin D, as has been proposed recently [19,20].

Impaired exocrine pancreatic function might also influence glucose control, since exocrine and endocrine

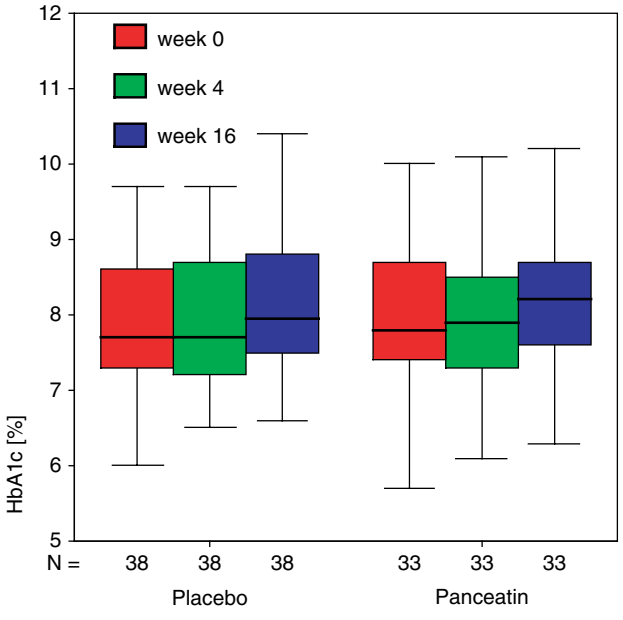


**Figure 2. $HbA_{1c}$ measured at weeks 0, 4 and 16 during treatment with pancreatin or placebo**

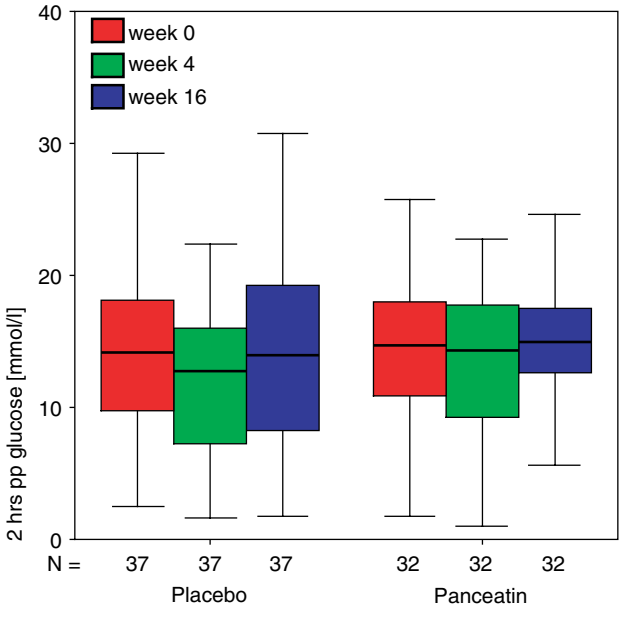


**Figure 3. 2-h glucose values following oral glucose load at weeks 0, 4 and 16 during treatment with pancreatin or placebo**



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**Table 1. Patients' symptoms (week 0, 16) as assessed by a standardised questionnaire**

| | Stool consistency | | | |
|---|---|---|---|---|
| | Week 0 | | Week 16 | |
| | Pancreatin | Placebo | Pancreatin | Placebo |
| Watery | 0 | 1 | 0 | 1 |
| Soft | 3 | 3 | 3 | 4 |
| Regular | 33 | 34 | 34 | 34 |
| Hard | 3 | 3 | 2 | 2 |
| Total | 39 | 41 | 39 | 41 |
| | **Flatulence** | | | |
| | Week 0 | | Week 16 | |
| | Pancreatin | Placebo | Pancreatin | Placebo |
| None | 13 | 16 | 14 | 15 |
| Mild | 24 | 21 | 23 | 24 |
| Moderate | 2 | 4 | 2 | 2 |
| Severe | 0 | 0 | 0 | 0 |
| Total | 39 | 41 | 39 | 41 |
| | **Abdominal pain** | | | |
| | Week 0 | | Week 16 | |
| | Pancreatin | Placebo | Pancreatin | Placebo |
| None | 34 | 29 | 35 | 34 |
| Mild | 4 | 12 | 4 | 6 |
| Moderate | 1 | 0 | 0 | 1 |
| Severe | 0 | 0 | 0 | 0 |
| Total | 39 | 41 | 39 | 41 |
| | **Global clinical impression assessed by the investigator** | | | |
| | Week 0 | | Week 16 | |
| | Pancreatin | Placebo | Pancreatin | Placebo |
| Good | 18 | 12 | 19 | 18 |
| Rather good | 18 | 25 | 17 | 21 |
| Rather bad | 3 | 4 | 1 | 2 |
| Bad | 0 | 0 | 2 | 0 |
| Total | 39 | 41 | 39 | 41 |
| | **Global clinical impression assessed by the patient** | | | |
| | Week 0 | | Week 16 | |
| | Pancreatin | Placebo | Pancreatin | Placebo |
| Good | 18 | 12 | 20 | 18 |
| Rather good | 18 | 24 | 15 | 20 |
| Rather bad | 3 | 5 | 2 | 2 |
| Bad | 0 | 0 | 2 | 1 |
| Total | 39 | 41 | 39 | 41 |
| | **Mean number of stools/die** | | | |
| | Pancreatin | | Placebo | |
| Week 0 | 1.27 | | 1.37 | |
| Week 16 | 1.54 | | 1.56 | |

**Table 2. Vitamin levels during treatment with pancreatin or placebo at weeks 0, 4, 10 and 16**

| | Vitamin A (µmol/L) | | | | |
|---|---|---|---|---|---|
| Treatment | | Week 0 | Week 4 | Week 10 | Week 16 |
| Placebo | Mean | 2.07 | 2.17 | 2.10 | 2.05 |
| | Std. deviation | 0.67 | 0.61 | 0.64 | 0.54 |
| Pancreatin | Mean | 2.05 | 2.12 | 2.01 | 2.02 |
| | Std. deviation | 0.49 | 0.74 | 0.61 | 0.66 |
| | **Vitamin D (nmol/L)** | | | | |
| Treatment | | Week 0 | Week 4 | Week 10 | Week 16 |
| Placebo | Mean | 60.20 | 55.63 | 61.78 | 62.70 |
| | Std. deviation | 24.09 | 22.84 | 26.13 | 26.25 |
| Pancreatin | Mean | 54.10 | 52.03 | 56.63 | 59.42 |
| | Std. deviation | 19.44 | 20.14 | 18.35 | 24.35 |
| | **Vitamin E (µmol/L)** | | | | |
| Treatment | | Week 0 | Week 4 | Week 10 | Week 16 |
| Placebo | Mean | 25.29 | 26.10 | 25.85 | 26.81 |
| | Std. deviation | 8.88 | 7.82 | 7.36 | 6.14 |
| Pancreatin | Mean | 25.69 | 25.69 | 25.81 | 27.45 |
| | Std. deviation | 5.64 | 6.88 | 7.34 | 7.70 |

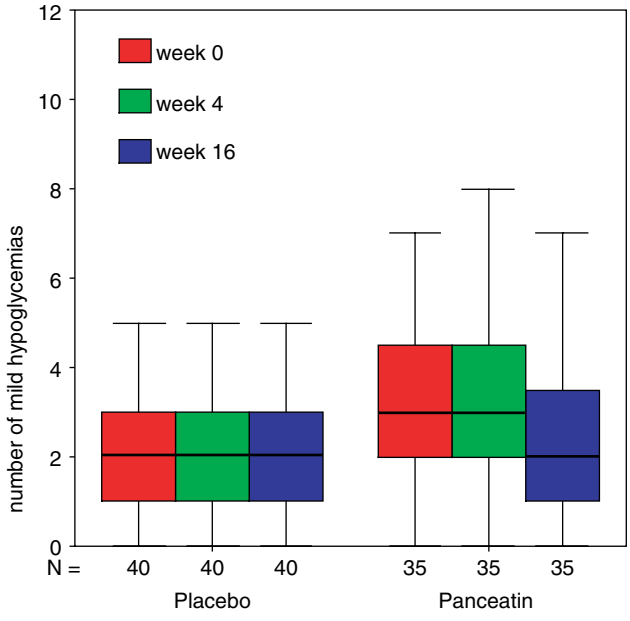


**Figure 4. Number of mild and moderate hypoglycemia reported during weeks 0, 4 and 16 during treatment with pancreatin or placebo**

pancreas are linked closely to anatomy and function [1,2,16,19]. In the present study, no beneficial effect of pancreatic enzyme replacement therapy on parameters of glucose metabolism could be observed. However, it has clearly been shown that enzyme replacement therapy can be used safely in diabetes mellitus and does not result in problems of diabetes control as reported in an earlier study [23]. In contrast, a reduction in mild and moderate hypoglycemia was observed in the treatment group, suggesting a more stable control of insulin therapy. Yet, it is important to mention that there was more mild and moderate hypoglycemia at the baseline in the



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pancreatin group as compared to that in the placebo group. After reduction in the pancreatin group, both groups were basically equal at the end of double-blind treatment ($p > 0.05$).

Although no relevant effects of pancreatin therapy on the parameters of glucose metabolism and clinical symptoms could be observed in this study on type 1 diabetes patients, it might be very interesting to use the same protocol in diabetic patients with exocrine insufficiency without insulin therapy (NIDDM). It is known that i.v. application of FFA leads to an increase in basal and stimulated insulin secretion by beta cells [21]. Since the same stimulatory effect on insulin secretion can be observed after oral application of FFA [25], qualitative fat maldigestion in patients with exocrine pancreatic insufficiency might be a relevant factor contributing to the development of diabetes mellitus. It is also known that, in gastrointestinal diseases accompanied by malabsorption, such as exocrine pancreatic insufficiency, nutrient-induced GIP (glucose-dependent insulinotropic polypeptide) response is diminished, leading to higher blood glucose levels and a worse glucose tolerance (incretin effect of fat). This effect was shown to be reversible by adequate pancreatic enzyme substitution therapy [26]. Yet, one has to also keep in mind that GLP-1 responses can be predicted to be more prominent under conditions of malassimilation [27], which might partially counteract the above-described effect.

Owing to the lack of effects of enzyme treatment on clinical symptoms in this study, it is important to keep in mind that about 60% of patients with reduced FEC have been reported to suffer from steatorrhea [19]. Therefore, about 40% of the patients are treated with enzyme replacement therapy in this study without subjectively requiring it for maintenance of normal digestion and absorption. This could explain the lack of effects on symptoms.

In summary, enzyme replacement therapy can be used safely in type 1 patients with pancreatic exocrine dysfunction. A clinical study on the possible effects of this therapy parameters on glucose metabolism should be performed in type 2 patients.

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