Prevalence And Clinical Relevance Of Exocrine Pancreatic Insufficiency In Diabetes Mellitus

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University Hospital Giessen and Marburg
Giessen, Germany
1. What is the prevalence of exocrine pancreatic insufficiency in diabetes mellitus?

2. Is diabetes mellitus secondary to pancreatic diseases (type-3) a frequent phenomenon?

3. What are the clinical consequences of exocrine pancreatic insufficiency in diabetes mellitus?
1. What is the prevalence of exocrine pancreatic insufficiency in diabetes mellitus?
## The prevalence of exocrine pancreatic insufficiency in diabetes mellitus

<table>
<thead>
<tr>
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<th>Year</th>
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<th>Methods</th>
<th>Results</th>
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<tbody>
<tr>
<td>Pollard H et al.</td>
<td>1943</td>
<td>13</td>
<td>Amylase and lipase after pancreozymin-secretin stimulation</td>
<td>62% reduced</td>
</tr>
<tr>
<td>Chey WY et al.</td>
<td>1963</td>
<td>50 diabetic patients; 13 juvenile type</td>
<td>Amylase and lipase after pancreozymin-secretin stimulation</td>
<td>Low amylase output in diabetes 36%; Juvenile diabetes 77%</td>
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<tr>
<td>Vacca JB et al.</td>
<td>1964</td>
<td>55 diabetic patients (22 insulin treated)</td>
<td>Diastase and bicarbonate after secretin stimulation; fecal fat</td>
<td>73% abnormal; correlation with age, no correlation with fecal fat</td>
</tr>
<tr>
<td>Frier BM et al.</td>
<td>1976</td>
<td>20 IDDM, 7 NIDDM, 13 controls</td>
<td>Stimulation with iv secretin and CCK-PZ</td>
<td>PEI: 80% IDDM; correlation with duration</td>
</tr>
<tr>
<td>Harano Y et al.</td>
<td>1978</td>
<td>53 NIDDM, 4 IDDM, 18 controls</td>
<td>Secretin-pancreozymin test</td>
<td>Diabetes: 69% deficient enzyme output; correlation with diabetes control</td>
</tr>
<tr>
<td>Lankisch PG et al.</td>
<td>1982</td>
<td>53 IDDM</td>
<td>Secretin-pancreozymin test</td>
<td>Diabetes: 43% impaired function</td>
</tr>
<tr>
<td>Bretzke G et al.</td>
<td>1984</td>
<td>60 insulin-treated type 2 diabetic patients</td>
<td>Secretin-pancreozymin test</td>
<td>Diabetes 27% „mild PEI”</td>
</tr>
<tr>
<td>El Nehwihi H et al.</td>
<td>1988</td>
<td>10 type 2 diabetic patients with diarrhea and neuropathy</td>
<td>Secretin and CCK test</td>
<td>Enzyme and bicarbonate reduction in all subjects</td>
</tr>
<tr>
<td>Semakula C</td>
<td>1996</td>
<td>307 IDDM, 303 non-diabetic siblings, 207 controls</td>
<td>Serum amylase and lipase</td>
<td>Reduced enzyme levels in 18% IDDM, 6% siblings and 2% controls</td>
</tr>
</tbody>
</table>

**Studies on function by direct function tests:**

Abnormal in 52.4% (18-100%)
The prevalence of exocrine pancreatic insufficiency in diabetes mellitus

<table>
<thead>
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<th>Author</th>
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<th>Results</th>
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</thead>
<tbody>
<tr>
<td>Hardt et al.</td>
<td>1999</td>
<td>128 type 1+2</td>
<td>Fecal chymotrysin</td>
<td>45% &lt; 6 U7l</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fecal elastase 1</td>
<td>46% &lt; 200 µg/g</td>
</tr>
<tr>
<td></td>
<td>2000</td>
<td>39 type 1</td>
<td>Fecal elastase 1</td>
<td>74% &lt; 200 µg/g</td>
</tr>
<tr>
<td></td>
<td></td>
<td>77 type 2</td>
<td></td>
<td>36%</td>
</tr>
<tr>
<td>Icks et al.</td>
<td>2001</td>
<td>112 type 1</td>
<td>Fecal elastase 1</td>
<td>54,5% &lt; 200 µg/</td>
</tr>
<tr>
<td>Rathmann et al.</td>
<td>2001</td>
<td>544 type 2</td>
<td>Fecal elastase 1</td>
<td>30,3% &lt; 200 µg/</td>
</tr>
<tr>
<td>Hardt et al.</td>
<td>2003</td>
<td>323 type 1</td>
<td>Fecal elastase 1</td>
<td>51% &lt; 200 µg/</td>
</tr>
<tr>
<td></td>
<td></td>
<td>697 type 2</td>
<td></td>
<td>35% &lt; 200 µg/</td>
</tr>
<tr>
<td>Nunes et al.</td>
<td>2003</td>
<td>42 type 1+2</td>
<td>Fecal elastase 1</td>
<td>36% &lt; 200 µg/g</td>
</tr>
<tr>
<td>Yilmaztepe et al.</td>
<td>2005</td>
<td>32 type 2</td>
<td>Fecal elastase 1</td>
<td>28% &lt; 200 µg/</td>
</tr>
<tr>
<td>Cavalot et al.</td>
<td>2006</td>
<td>66 type 1</td>
<td>Fecal elastase 1</td>
<td>26% &lt; 200 µg/g</td>
</tr>
</tbody>
</table>

Studies on function by indirect function tests:
Abnormal in type 1 diabetes: 51% (26-74%)
Abnormal in type 2 diabetes: 32% (28-36%)
High Prevalence of Exocrine Pancreatic Insufficiency in Diabetes mellitus

A Multicenter Study Screening Fecal Elastase 1 Concentrations in 1,021 Diabetic Patients

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\textsuperscript{a}Third Medical Department and Policlinic, Giessen University Hospital, Giessen and \textsuperscript{b}Hochschulrechenzentrum, Giessen University, Giessen, Germany
Characteristics and clinical findings in type 1 (a) and type 2 (b) diabetes mellitus patients

<table>
<thead>
<tr>
<th></th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>19</td>
<td>74</td>
<td>41.6</td>
<td>0.62</td>
</tr>
<tr>
<td>Diabetes duration, years</td>
<td>&lt;1</td>
<td>46</td>
<td>16.1</td>
<td>0.61</td>
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<tr>
<td>Age at onset, years</td>
<td>1</td>
<td>70</td>
<td>25.6</td>
<td>0.73</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>15.8</td>
<td>37.5</td>
<td>25.21</td>
<td>0.18</td>
</tr>
<tr>
<td>Fecal elastase 1, µg/g</td>
<td>4</td>
<td>719</td>
<td>223.2</td>
<td>8.9</td>
</tr>
<tr>
<td><strong>Type 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>21</td>
<td>78</td>
<td>53.8</td>
<td>0.28</td>
</tr>
<tr>
<td>Diabetes duration, years</td>
<td>&lt;1</td>
<td>39</td>
<td>8.7</td>
<td>0.28</td>
</tr>
<tr>
<td>Age at onset, years</td>
<td>13</td>
<td>67</td>
<td>45.1</td>
<td>0.33</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>18.5</td>
<td>69.4</td>
<td>29.5</td>
<td>0.18</td>
</tr>
<tr>
<td>Fecal elastase 1, µg/g</td>
<td>0</td>
<td>877</td>
<td>304.1</td>
<td>7.41</td>
</tr>
</tbody>
</table>

*a Type 1: n = 323; 115 (35.6%) female, 208 (64.4%) male; 1 (0.3%) diet, 322 (99.7%) insulin.
*b Type 2: n = 697; 218 (31.3%) female, 479 (68.7%) male; 331 (47.5%) diet/OAD, 366 (52.5%) insulin.

SEM = Standard error of the mean. One patient had not yet been classified as type 1 or type 2 diabetes mellitus.
Exocrine function in diabetes mellitus as determined by fecal elastase 1 concentrations

**Type 1 (n = 323)**
- Severe insufficiency: 28.5%
- Mild insufficiency: 22.6%
- Normal: 48.0%
- Missing data: 0.9%

**Type 2 (n = 697)**
- Severe insufficiency: 19.9%
- Mild insufficiency: 15.5%
- Normal: 64.1%
- Missing data: 0.4%

*Hardt PD et al., Pancreatology 3: 395-402, 2003*
The prevalence of morphologic changes of the exocrine pancreas in diabetes mellitus are frequent. The prevalence is about 40% (11-75%). Changes are more pronounced in type 1.
Summary I:

The prevalence of exocrine pancreatic insufficiency is very high in diabetic populations:

NIDDM/Type 2: about 35% (15-73) exocrine insufficiency
IDDM/Type 1: about 50% (40-80) exocrine insufficiency using indirect as well as direct function tests.

The prevalence of morphologic changes is also rather common and affects up to 40%.
2. Is diabetes mellitus secondary to pancreatic disease (type-3) a frequent phenomenon?
Exocrine dysfunction in diabetes mellitus: Pathophysiological concepts - 1

(1) Insulin has a trophic effect on pancreatic acinar tissue (insulin-acinar portal system) and its lack may cause pancreatic atrophy
  *Williams JA, Goldfine ID (1985); Korc M (1993)*

(2) Islet hormones have regulatory functions on exocrine tissue which may be impaired
  *Lazarus SS and Volk BW (1961); Adler G, Kern HF (1975)*

(3) Diabetic autonomic neuropathy may lead to impaired enteropancreatic reflexes and exocrine dysfunction
  *El Newihi H et al. (1988)*
Exocrine dysfunction in diabetes mellitus: Pathophysiologica concepts - 2

(4) Diabetic angiopathy may cause local microangiopathy followed by pancreatic fibrosis and atrophy
Warren S, Le Compte PM (1952); Vacca JB et al. (1964)

(5) Elevated hormone and peptide concentrations (glucagon, pancreatic polypeptide P, somatostatin) may suppress exocrine function
Lazarus SS, Volk BW (1958); Dyck WP et al. (1969); Unger RH et al. (1970); Patel JY, Weir GC (1976); Korc M (1993)
Exocrine dysfunction in diabetes mellitus: Pathophysiologica l concepts - 3

(6) Simultaneous damage of exocrine and endocrine tissue:

a Viral infections
Gamble DR et al. 1973; Sanvito F et al. 1995; Mally IM et al. 1996

b Simultaneous damage by autoimmunity
Kobayashi T et al. 1990; Taniguchi T et al. 2003

c Genetic changes affecting exocrine and endocrine tissue
Raeder et al. 2006

d Altered beta cell regeneration from exocrine/ductal tissue
Exocrine dysfunction in diabetes mellitus – pathophysiological concepts

(7) „...it is also possible that some of the diabetics are actually patients with chronic pancreatitis. It is this that we would emphasize.“

[Chey et al. 1963]
Pancreatic diseases as a cause of diabetes mellitus

**Prevalence:**
Pancreatic diabetes is believed to account for only 0.5%–1.15% of all patients with diabetes mellitus.

[Alberti 1988; Günther 1961]
**I. Type 1 diabetes** (β-cell destruction, usually leading to absolute insulin deficiency)

A. Immune mediated

B. Idiopathic

**II. Type 2 diabetes** (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)

**III. Other specific types**

A. Genetic defects of β-cell function

B. Genetic defects in insulin action

C. **Diseases of the exocrine pancreas**

D. Endocrinopathies

E. Drug- or chemical-induced

F. Infections

G. Uncommon forms of immune-mediated diabetes

H. Other genetic syndromes sometimes associated with diabetes

**IV. Gestational diabetes mellitus (GDM)**

*[Diabetes Care 26:S5-S20, 2003]*
Pancreatic diseases as a cause of diabetes mellitus

- acute pancreatitis
- chronic pancreatitis
- carcinoma
- surgery
- hemochromatosis
- cystic fibrosis
Diabetes mellitus in pancreatitis

Prevalence of diabetes mellitus in **acute pancreatitis**:
- about 50% impaired glucose tolerance during acute phase
- **persisting diabetes in 1-5%**
  [Warren et al. 1950, Scuro et al. 1984]

Prevalence of diabetes mellitus in **chronic pancreatitis**:
- 40-70%
- in chronic-calcifying pancreatitis up to 90%
  [Bank et al. 1975]
Is pancreatic diabetes (type-3 diabetes) more common than believed so far?

The definition of chronic pancreatitis includes persisting/progressive changes of exocrine function and morphology.

A significant number of diabetes patients not only show functional changes, but morphologic changes matching diagnostic criteria for chronic pancreatitis.
Reclassification study

- Retrospective analysis of 1922 patients with diabetes mellitus

- Screening patients records for parameters of exocrine function and morphology, diabetes duration, diabetes therapy, age at onset, C-peptide levels, HbA1c levels, and diabetes associated antibodies

- Diagnosis type 1: Presence of autoantibodies, early onset, early insulin requirement
  Diagnosis type 2: absence of autoantibodies, no (late) insulin requirement, insulin resistance
  Diagnosis type 3: Absence of autoantibodies, exocrine pancreatic insufficiency, typical morphologic findings

[Ewald et al., submitted]
Prevalence of pancreatic diabetes (Type IIIC) in 1922 patients of a university hospital

8% Type 3 diabetes mellitus
92% Type 1 or type 2 diabetes mellitus

[Ewald et al., submitted]
Etiology of pancreatic diabetes (Type IIIc) in 1922 patients of a university hospital

- Chronic pancreatitis: 76%
- Hemochromatosis: 9%
- Pancreatic cancer: 8%
- Cystic fibrosis: 4%
- Pancreas surgery: 3%

[Ewald et al., submitted]
Invalid classification of patients with type 3 diabetes mellitus:

- Classified as type 2: 80%
- Classified as type 1: 12%
- No classification: 8%

[Source: Ewald et al., submitted]
How can type-3 diabetes mellitus be frequent if the incidence of chronic pancreatitis is believed to be as low as 0.2 to 8 per 1000 inhabitants in clinical studies?

[Gullo et al. 1977; Andersen et al. 1982]
Chronic pancreatitis and type-3 diabetes mellitus appear to be underestimated in clinical studies compared to autopsies:

3821 autopsy cases:
- 5.3% CP of non-diabetic persons at autopsy
- 11.2% CP of diabetic persons at autopsy

[Blumenthal et al, Arch Surg 1963]

394 autopsy cases:
- 2 (0.5%) had clinical chronic pancreatitis
  13% had CP at autopsy
  19% of patients with CP at autopsy had clinical diabetes
  7% of cases without CP at autopsy had clinical diabetes

Could the diagnosis of chronic pancreatitis be missed in clinical practice?

- Symptoms of exocrine disease are not specific in the early stages of chronic pancreatitis.

- Since diagnostic procedures have historically been rather invasive (ERCP, direct function tests) their use has been restricted to obvious indications.

- Endocrine dysfunction should be expected to be diagnosed early and might be the first symptom recognized by patients and physicians.
Could the diagnosis of chronic pancreatitis be missed in clinical practice?

- In pancreatic diabetes, the clinical diagnosis of endocrine disease might be made first

- Patients might be misclassified as type-1 or type-2 diabetes mellitus
Could the diagnosis of chronic pancreatitis be missed in clinical practice?

73 patients with morphological signs of CP and moderate exocrine insufficiency (secretin test)
- 40% diabetic
- 54% impaired glucose tolerance
- 20% steatorrhea

[Aparisi et al. Med Clin Barc 2001]
Summary II

Is diabetes mellitus secondary to pancreatic disease a frequent phenomenon?

Yes!
Type-3 diabetes mellitus appears to be much more frequent than 0.5-1.15% of diabetes cases. According to recent data it might represent 8% of all cases with diabetes mellitus!
Consequences:

- Diagnostic concepts should be changed to detect exocrine disease at earlier stages
- Prevention and early treatment of exocrine disease might prevent progression to diabetes mellitus
- Type-3 diabetes should be studied more carefully to consider peculiarities of this disease
3. What are the clinical consequences of exocrine pancreatic insufficiency in diabetes mellitus?
High Prevalence of Steatorrhea in 101 Diabetic Patients Likely to Suffer from Exocrine Pancreatic Insufficiency According to Low Fecal Elastase 1 Concentrations

A Prospective Multicenter Study

PHILIP D. HARDT, MD, ANNETTE HAUENSCHILD, PhD, CLEMENS JAEGGER, MD, JOACHIM TEICHHMANN, MD, REINHARD G. BRETZEL, MD, HANS U. KLOER, MD, and THE S2453112/S2453113 STUDY GROUP
Study protocol

- 101 patients (30 type-1; 71 type-2) fecal elastase 1 concentrations < 100 µg/g
- fat standardized nutrition (100 g/die) for 4 days
- complete stool collection last 72 hrs
- documentation of clinical parameters and symptoms
- analysis of fat excretion according to Van de Kamer
## Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>50.77 ± 9.26</td>
<td>25</td>
<td>74</td>
</tr>
<tr>
<td>BMI</td>
<td>28.26 ± 3.6</td>
<td>20.9</td>
<td>36.86</td>
</tr>
<tr>
<td>FEC (µg/g)</td>
<td>56.03 ± 27.06</td>
<td>5</td>
<td>100</td>
</tr>
<tr>
<td>Diabetes duration (yr)</td>
<td>10.1 ± 8.32</td>
<td>0</td>
<td>39</td>
</tr>
</tbody>
</table>

*There were 28 women, 73 men; 30 with type 1, and 71 type 2 diabetes. FEC = fecal elastase 1 concentration.*
Clinical Findings in Diabetic Patients with Fecal Elastase 1 Concentrations < 100 µg/g

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD*</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFA* (%)</td>
<td>91.79 ± 5.22</td>
<td>76</td>
<td>98.5</td>
</tr>
<tr>
<td>Fat intake (g/day)</td>
<td>118.87 ± 26.8</td>
<td>49.6</td>
<td>224.1</td>
</tr>
<tr>
<td>Fat excretion (g/day)</td>
<td>9.19 ± 5.39</td>
<td>1.4</td>
<td>31.3</td>
</tr>
<tr>
<td>Stool weight (g/day)</td>
<td>185.7 ± 100.1</td>
<td>47.6</td>
<td>669.2</td>
</tr>
</tbody>
</table>

*CFA = coefficient of fat absorption.

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of stools (N=)</td>
<td>76.9%</td>
<td>20.2%</td>
<td>1.9%</td>
<td>1%</td>
</tr>
<tr>
<td>Stool consistency*</td>
<td>64.4%</td>
<td>8.7%</td>
<td>26.9%</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain†</td>
<td>87.5%</td>
<td>10.6%</td>
<td>1.9%</td>
<td></td>
</tr>
<tr>
<td>Flatulence‡</td>
<td>42.3%</td>
<td>39.4%</td>
<td>16.4%</td>
<td>1.9%</td>
</tr>
</tbody>
</table>

*1 = formed/normal; 2 = hard; 3 = soft.
†1 = none; 2 = mild; 3 = moderate.
‡1 = none; 2 = mild; 3 = moderate; 4 = severe.

Fat digestion in Diabetes mellitus

Proportion of normal and pathologic fat digestion in 101 patients with diabetes mellitus and fecal elastase 1 concentrations < 100 µg/g

>10 g/die
39,6%

7-10 g/die
19,8%

< 7 g/die (normal)
40,6%

[Hardt et al., Dig Dis Sci 2003]
Follow-up of exocrine pancreatic function in type-1 diabetes mellitus.

- Follow up of 20 out of 53 patients from an earlier study
- Pancreatic insufficiency by secretin-pancreozymin test
- no correlation between diabetes duration and test results
- in 2 cases progress to PEI
- in 2 patients normalisation

„Therefore, this finding is of minor clinical importance and expensive pancreatic enzyme substitution will not be required.“

[Creutzfeldt et al., Digestion. 2005]
The main messages of this study are that

1) 29% of asymptomatic type 1 diabetic patients negative for autoantibodies associated with celiac disease present steatorrhea,

2) FFE inversely correlates to PE-1, and

3) steatorrhea occurs in 22% of patients with normal PE-1.

Our study therefore shows that PE-1 is associated with steatorrhea but to an extent too weak to justify measurement of FFE only in patients with low PE-1.“
Steatorrhea is common in patients with diabetes mellitus and exocrine insufficiency!!!
Steatorrhea in diabetes mellitus – consequences?

- Do diabetic patients show clinical symptoms and do symptoms correlate with the degree of steatorrhea?

- Can steatorrhea in diabetes mellitus be treated with enzyme replacement therapy?

- Do diabetic patients show qualitative malnutrition (deficiency of fat-soluble nutrients, e.g. vitamin D)?

- Is there an impact of fat maldigestion on glucose metabolism?

- Should steatorrhea in diabetes mellitus be treated with enzyme replacement therapy?
Steatorrhea and symptoms
in 101 diabetic patients with fecal elastase < 100 µg/g

<table>
<thead>
<tr>
<th>Fat Excretion</th>
<th>Abdominal Pain</th>
<th>Stool Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 7 g/d</td>
<td>No correlation</td>
<td>No correlation</td>
</tr>
<tr>
<td>7-10 g/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 10 g/d</td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Fat Excretion</th>
<th>Stool Consistency</th>
<th>Meteorism/Flatulence</th>
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</thead>
<tbody>
<tr>
<td>&lt; 7 g/d</td>
<td>sign. correlation</td>
<td>sign. correlation</td>
</tr>
<tr>
<td>7-10 g/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 10 g/d</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

p < 0.05

[Hardt et al., submitted]
There is an association between clinical symptoms of exocrine insufficiency and the degree of steatorrhea.
Can steatorrhea be treated in diabetic patients?

**German multicenter study:**
- 29 patients with fecal fat excretion > 10 g/day
- Run-in-phase: fat standardized nutrition (100 g/die) for 4 days
- Treatment-phase: fat standardized nutrition (100 g/die) for 4 days
- Randomization to receive either minimicropheres pancreatin (10000 lipase units) \( n = 16 \) or placebo \( n = 13 \) 15 capsules/die
- Complete stool collection last 72 hrs
- Documentation of clinical parameters and symptoms
- Analysis of fat excretion according to Van de Kamer

[Hardt et al., submitted]
Can steatorrhea be treated in diabetic patients?

<table>
<thead>
<tr>
<th></th>
<th>Pancreatin (n=16)</th>
<th>Placebo (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>fecal fat (run-in)</td>
<td>13.4 g/d (+/-3.9)</td>
<td>12.4 g/d (+/-3.2)</td>
</tr>
<tr>
<td>fecal fat (treatment)</td>
<td>6.9 g/d (+/-2.3)</td>
<td>11.4 g/d (+/-5.7)</td>
</tr>
</tbody>
</table>

p < 0.05

no relevant side-effects or adverse events observed

[Hardt et al., unpublished data]
In patients with diabetes mellitus and exocrine insufficiency steatorrhea can be treated by enzyme replacement therapy. The treatment appears to be safe.

[Hardt et al., unpublished data]
## Symptoms and treatment (n = 29)

**Stool consistency**

<table>
<thead>
<tr>
<th></th>
<th>hard n (%)</th>
<th>normal n (%)</th>
<th>soft n (%)</th>
<th>watery n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Run in:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control group</td>
<td>0 (0)</td>
<td>8 (66.7)</td>
<td>4 (33.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pancreatin group</td>
<td>2 (13.3)</td>
<td>10 (66.7)</td>
<td>3 (20.0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Treatment:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control group</td>
<td>1 (8.3)</td>
<td>8 (66.7)</td>
<td>3 (25)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pancreatin group</td>
<td>1 (6.7)</td>
<td>13 (86.7)</td>
<td>1 (6.7)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

* p > 0.05

**Flatulence / meteorism**

<table>
<thead>
<tr>
<th></th>
<th>None n (%)</th>
<th>Mild n (%)</th>
<th>Moderate n (%)</th>
<th>Severe n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Run in:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control group</td>
<td>5 (41.7)</td>
<td>4 (33.3)</td>
<td>3 (25.0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pancreatin group</td>
<td>4 (26.7)</td>
<td>9 (60.0)</td>
<td>1 (6.7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Treatment:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control group</td>
<td>4 (33.3)</td>
<td>3 (25.0)</td>
<td>5 (41.7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pancreatin group</td>
<td>7 (46.7)</td>
<td>5 (33.3)</td>
<td>3 (20.0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

* p > 0.05

**Abdominal pain**

<table>
<thead>
<tr>
<th></th>
<th>None n (%)</th>
<th>Mild n (%)</th>
<th>Moderate n (%)</th>
<th>Severe n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Run in:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control group</td>
<td>11 (91.7)</td>
<td>1 (8.3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pancreatin group</td>
<td>13 (86.7)</td>
<td>2 (13.3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Treatment:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control group</td>
<td>11 (91.7)</td>
<td>1 (8.3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pancreatin group</td>
<td>13 (86.7)</td>
<td>2 (13.3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

* p > 0.05

[Hardt et al., submitted]
Clinical symptoms improved under enzyme therapy, however the difference was not statistically significant due to small patient numbers.
Steatorrhea and qualitative malnutrition:

A significant correlation between reduced fecal elastase 1 levels and low vitamin D levels has been demonstrated e.g. in osteoporosis

[Mann et. al. 2003]

Vitamin D plays a role in the regulation/function of the immune system and vitamin D deficiency might be involved in the pathogenesis of type 1 diabetes

[Holick 2004; Virtanen et al. 2003]
Steatorrhea and qualitative malnutrition in diabetes mellitus: “The Canada study“

Patients with insulin treated diabetes and fecal elastase 1 < 100 µg/g (n=80); 16 weeks of treatment with pancreatin vs placebo

Levels of vitamins E,D and A within the normal range

Vitamin A levels unchanged in both groups

Vitamin D levels increased in treatment group

Vitamin E levels increased in both groups

No significant differences between groups

[Hardt et al., submitted]
Studies on enzyme replacement therapy in patients with diabetes mellitus and exocrine pancreatic insufficiency with regard to glucose metabolism:

- No positive effect on HbA1c; less stable control in patients with diabetes in chronic pancreatitis [O´Keefe et al. J Clin Gastroenterol 2001]


- No positive effect on HbA1c but more stable control in patients classified as insulinopenic diabetes in CP [Glasbrenner et al. Z Gastroenterol 1990]
Enzyme replacement therapy in patients with diabetes mellitus and exocrine pancreatic insufficiency: “The Canada Study“

- Patients with insulin treated diabetes and fecal elastase 1 < 100 µg/g

- 39 pat. randomized to pancreatin; 41 pat. to placebo

- 16 weeks enzyme therapy and follow up

[Hardt et al., submitted]
The Canada Study

Pancreatin Placebo

HbA1c [%]

12 11 10 9 8 7 6 5

week 0 week 4 week 16

Insulin [U/day]

140 120 100 80 60 40 20 0

week 0 week 4 week 16

2 hrs pp glucose [mmol/l]

40 30 20 10 0

week 0 week 4 week 16

number of mild hypoglycemias

12 10 8 6 4 2 0

week 0 week 4 week 16

[Hardt et al., submitted]
In insulin-treated patients with diabetes mellitus and exocrine pancreatic insufficiency no obvious benefit nor negative effect regarding the control of glucose metabolism could be observed under enzyme replacement therapy.
What about glucose metabolism in patients with preserved beta-cell function and exocrine pancreatic insufficiency?
Incretins (e.g. GLP-1 and GIP) are secreted in response to oral feeding by special gut cells (K-duodenum (GIP); L-ileum/colon (GLP-1)).

Incretins augment beta cell insulin secretion after oral feeding (glucose, fat, protein) as compared to i.v. application of glucose.

In type-2-diabetes, GLP-1 secretion is reduced, the effects normal. GIP-secretion is normal, while effects are reduced.

[Holst et al. 2003]
The incretin-effect in pancreatic steatorrhea:

- 16 patients with chronic pancreatitis and steatorrhea (>25g/d)

- Liquid test meal with and without pancreatin

- Measurement of GIP, insulin and glucose

[Ebert and Creutzfeldt, Diabetologia 1980]
[Ebert and Creutzfeldt, Diabetologia 1980]
Incretin levels in pancreatitis compared to controls

- 28 patients with chronic pancreatitis/12 healthy controls

- GIP response to a test meal reduced as compared to healthy controls

- Lowest GIP-values in patients with CP and diabetes mellitus

[Gomez-Cerezo et al. 1996]
- In patients with steatorrhea the GIP-response after ingestion of nutrients is reduced

- Substitution of pancreatic enzymes improves digestion and GIP secretion

- The insulin response and glucose tolerance are also improved

[Creutzfeldt and Nauck 1992]
Is there an impact of fat maldigestion on glucose metabolism?

Yes: exocrine insufficiency can affect glucose metabolism in some cases of diabetes mellitus.

More studies are needed to learn about the quantitative relevance of this problem and the interactions of fat maldigestion and insulin secretion.
Should exocrine insufficiency and steatorrhea be treated by enzyme therapy in diabetes mellitus?

- No general recommendation so far
- Treatment, if steatorrhea and symptoms are present
- More studies on the impact on glucose metabolism and on qualitative malnutrition needed
Summary III

What are clinical consequences of exocrine pancreatic insufficiency in diabetes mellitus?

- Steatorrhea, GI-symptoms, impaired control of glucose metabolism, qualitative malnutrition
1. What is the prevalence of exocrine pancreatic insufficiency in diabetes mellitus?
   It is as high as 35% in patients previously classified as „type 2“ and about 50% in patients previously classified as „type 1“.

2. Is diabetes mellitus secondary to pancreatic diseases (type-3) a frequent phenomenon?
   It appears to affect at least 8% of all diabetic patients. A careful workup of every diabetic patient concerning the exocrine pancreas is recommended. More studies are needed in this field.

3. What are the clinical consequences of exocrine pancreatic insufficiency in diabetes mellitus?
   Steatorrhea is frequent in patients with diabetes mellitus. Fecal elastase 1 measurement can be used as a screening tool. PEI might be associated with symptoms and can affect glucose control. More studies are of great interest and clinical relevance.
Thank you for the Audience

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