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Endocrine & Exocrine Insufficiency in Chronic Pancreatitis

What a Diabetologist should now

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SFD Karlstad 2023

Disclaimer

- Honoraria
  →Abbott, Mylan, Viatris

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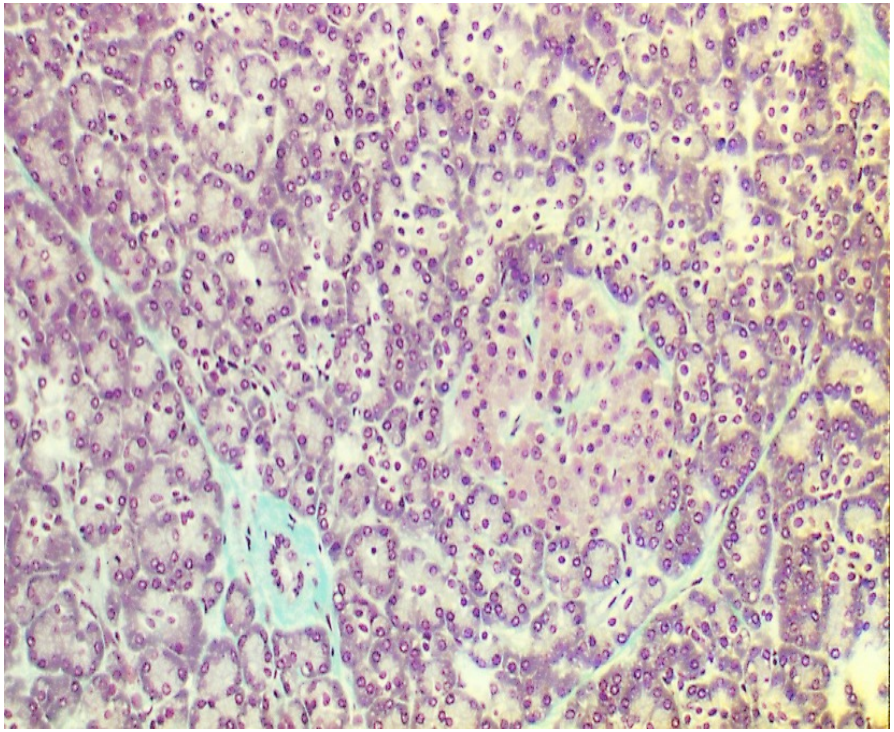
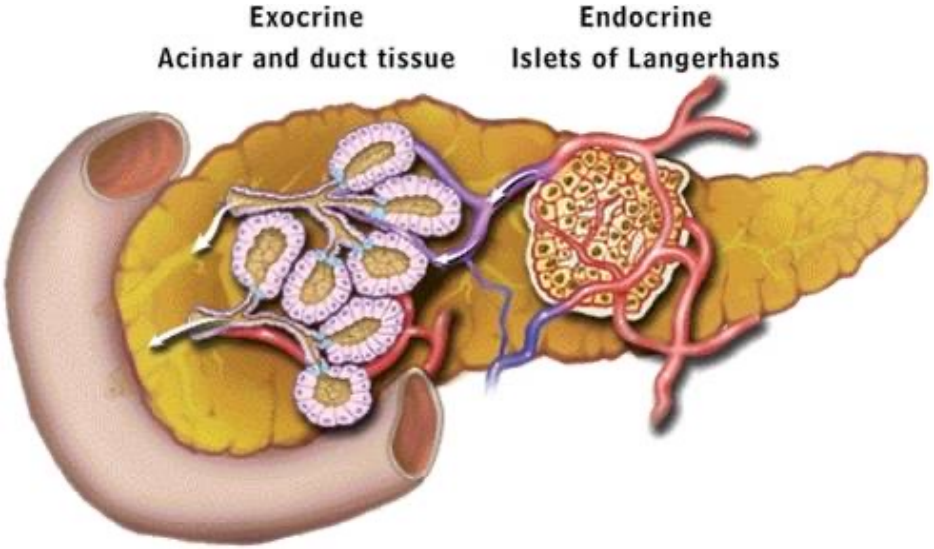
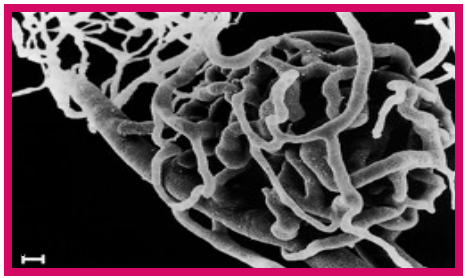
Diabetes mellitus and PEI

The endocrine and exocrine pancreas “reside” next to each other



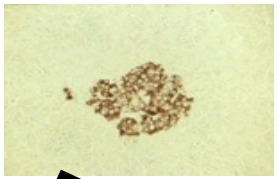


Islet-acinar axis in diabetes



Insulo-acinar portal system:
Exocrine pancreas exposed to high concentrations of islet hormones

Healthy subjects



Insulin

Trophic effects

Halo phenomenon

Enzyme release in response to stimulants ↑

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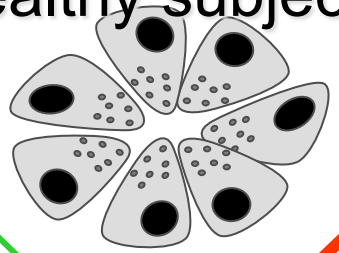


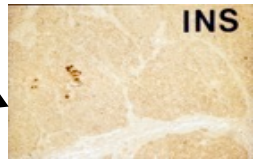
+

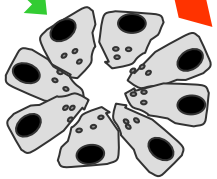
Glucagon, SST, PP

Atrophic effects

Inhibition of exocrine function

Reduction to 0-5% in type I (IDDM)





Diabetics

- Atrophy
- Loss of halos
- **Exocrine insufficiency**

Löhr & Klöppel, Diabetologia 1987, 30: 757-762

Keller & Layer Gut 2005;54:Suppl 6: vi9-29

Pancreatogenic diabetes mellitus

Pancreatology

Review

Pancreatology 2011;11:279–294
DOI: 10.1159/000329188

Published online: July 9, 2011

Pancreatogenic Diabetes: Special Considerations for Management

YunFeng Cui[a, b] Dana K. Andersen[a]

[a]Department of Surgery, Johns Hopkins Bayview Medical Center, Johns Hopkins University School of Medicine, Baltimore, Md., USA; [b]Department of Surgery, Tianjin Nankai Hospital, Nankai Clinical School of Medicine, Tianjin Medical University, Tianjin, China

Table 1. Clinical and laboratory findings in types of diabetes mellitus

Parameter	Type 1 IDDM juvenile onset	Type 2 NIDDM adult onset	Type 3c pancreatogenic postop. onset
Ketoacidosis	common	rare	rare
Hyperglycemia	severe	usually mild	mild
Hypoglycemia	common	rare	common
Peripheral insulin sensitivity	normal or increased	decreased	increased
Hepatic insulin sensitivity	normal	normal or decreased	decreased
Insulin levels	low	high	low
Glucagon levels	normal or high	normal or high	low
PP levels	normal or low (late)	high	low
GIP levels	normal or low	normal or high	low
GLP-1 levels	normal	normal or high	normal or high
Typical age of onset	childhood or adolescence	adulthood	any

Low PP indicative of **Type 3c** diabetes mellitus

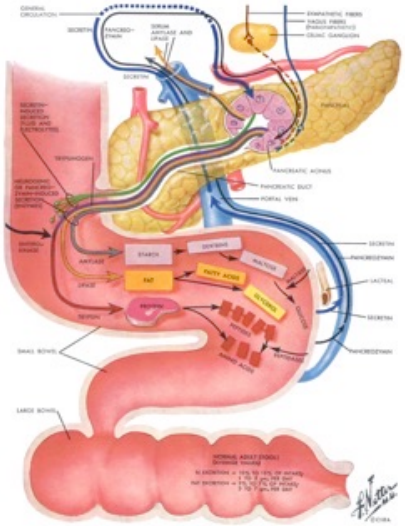
Pancreatology 2011;11:279-294

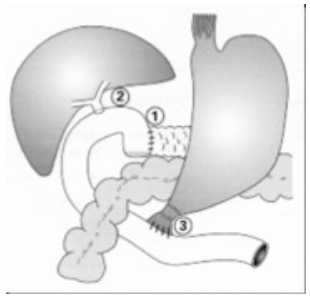
Pancreatic Exocrine Insufficiency (PEI)

Classification

Primary problem is in the pancreas
- destruction
- innervation

Secondary enzymes are released but do not work
- anatomical changes
- dysregulated activation
- dysregulated inactivation





uegj 2013, 1: 79-83

JOP. J Pancreas (Online) 2016 Mar 08; 17(3):216.

REVIEW ARTICLE

Prevalence of PEI in DM

Exocrine Pancreatic Insufficiency and Diabetes Mellitus

Miroslav Vujasinovic[1], Jana Makuc[2], Bojan Tepes[3]

Table 1. Characteristics of the included studies.

Study	Year	Country	Number of Participating Centres	Method Used To Diagnose EPI	Prevalence of EPI (%)
Chey [11]	1963	USA	1	secretin-pancreozymin test	37.5
Lankisch [16]	1982	Germany	1	secretin-pancreozymin test	43
el Newihi [2]	1988	USA	1	secretin and cholecystokinin test	100 (in all patients enzyme and bicarbonate reductions were found)
Hardt [4]	2000	Germany	1	faecal elastase 1	56.7 in type 1 DM 35.0 in type 2 DM
Icks [12]	2001	Germany	3	faecal elastase 1	45.5
Rathmann [21]	2001	Germany England	41 general practices	faecal elastase 1	30.3
Hardt [5]	2003	Germany	10	faecal elastase 1	51.1 in type 1 DM 35.4 in type 2 DM
Nunes [23]	2003	Portugal	1	faecal elastase 1	36
Cavalot [6]	2004	Italy	1	faecal elastase 1	56.7
Yilmaztepe [19]	2005	Turkey	1	faecal elastase 1	28.1
Larger [22]	2012	France	1	faecal elastase 1 and chymotrypsin	34-39% in type 1 DM 20% in type 2 DM
Vujasinovic [13]	2013	Slovenia	1	faecal elastase 1	5.4
Terzin [24]	2014	Hungary	1	faecal elastase 1	16.8
Shivaprasad [65]	2015	India	2	faecal elastase 1	31.4 in type 1 DM 29.4 in type 2 DM

30 - >50%

Post-pancreatitis diabetes mellitus – Karolinska

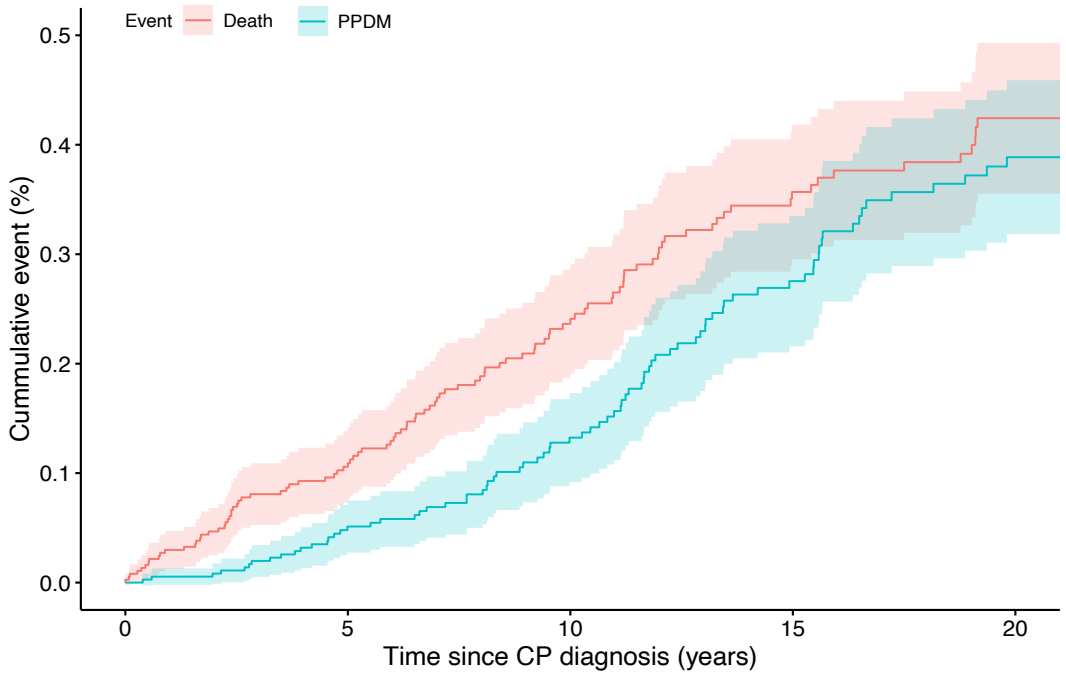
Received: 1 August 2022 | Accepted: 20 October 2022
DOI: 10.1002/ueg2.12344

ORIGINAL ARTICLE

ueg journal WILEY

Post-pancreatitis diabetes mellitus is common in chronic pancreatitis and is associated with adverse outcomes

Ana Dugic[1] | Hannes Hagström[1,2,3] | Ingrid Dahlman[1] | Wiktor Rutkowski[1] | Diana Daou[1] | Paula Kulinski[1] | J.-Matthias Löhr[2,4] | Miroslav Vujasinovic[1,2]



Cumulative incidence of PPDM in patients with CP derived from cumulative incidence function.
The green line shows cumulative incidence of PPDM after accounting for competing risk event (i.e., death occurring prior to the event of interest, presented by the red line).

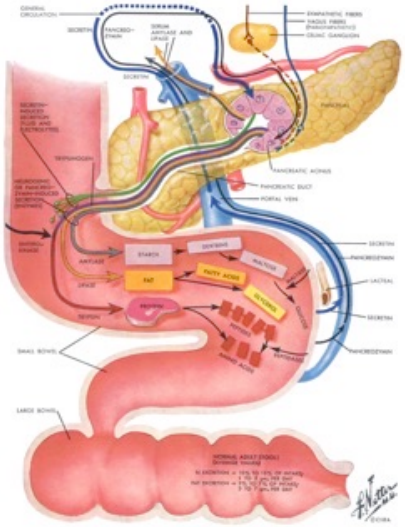
Accounted cumulative incidence for PPDM was 5.1%, 13.2%, 27.5%, and 38.9% at 5, 10, 15, and 20 years after CP diagnosis.

Pancreatic Exocrine Insufficiency (PEI)

Classification

Primary problem is in the pancreas

- **Autoimmune pancreatitis**
- Pancreatic cancer
- Diabetes mellitus



ARTHRITIS & RHEUMATOLOGY
Vol. 67, No. 7, July 2015, pp 1688–1699
DOI 10.1002/art.39132

INTERNATIONAL SYMPOSIUM on IgG4-RD & Fibrosis

KAROLINSKA UNIVERSITETSSJUKHUSET

SPECIAL ARTICLE

International Consensus Guidance Statement on the Management and Treatment of IgG4-Related Disease

A. Khosroshahi,[1] Z. S. Wallace,[2] J. L. Crowe,[3] T. Akamizu,[4] A. Azumi,[5] M. N. Carruthers,[6] S. T. Chari,[7] E. Della-Torre,[8] L. Frulloni,[9] H. Goto,[10] P. A. Hart,[11] T. Kamisawa,[12] S. Kawa,[13] M. Kawano,[14] M. H. Kim,[15] Y. Kodama,[16] K. Kubota,[17] M. M. Lerch,[18] M. Löhr,[19] Y. Masaki,[20] S. Matsui,[21] T. Mimori,[16] S. Nakamura,[22] T. Nakazawa,[23] H. Ohara,[23] K. Okazaki,[24] J. H. Ryu,[7] T. Saeki,[25] N. Schleinitz,[26] A. Shimatsu,[27] T. Shimosegawa,[28] H. Takahashi,[29] M. Takahira,[14] A. Tanaka,[30] M. Topazian,[7] H. Umehara,[20] G. J. Webster,[31] T. E. Witzig,[7] M. Yamamoto,[29] W. Zhang,[32] T. Chiba,[16] and J. H. Stone[2]

- **AIP** is considered a serious conditions triggering urgent intervention

Table 4. IgG4-related disease manifestations in which urgent treatment is recommended

Manifestation	Rationale for urgent treatment
Aortitis	Inflammatory aortic aneurysms can continue to enlarge and are at risk for dissection.
Retroperitoneal fibrosis	Progressive disease may lead to irreversible nerve damage/pain and/or ureteral obstruction/renal failure.
Proximal biliary strictures*	Untreated disease may lead to superimposed infectious cholangitis and eventually irreversible fibrosis and cirrhosis.
Tubulointerstitial nephritis	Untreated disease may lead to irreversible chronic kidney disease.
Pachymeningitis	Untreated disease puts the patient at risk for neurologic deficits and/or seizures.
Pancreatic enlargement	Untreated disease may lead to irreversible pancreatic exocrine and endocrine failure.
Pericarditis	Untreated disease may lead to tamponade or constrictive pericarditis

* "Proximal" denotes involvement of the intrahepatic bile ducts or extrahepatic portion of the common bile duct that is superior to the intrapancreatic portion.

UNITED EUROPEAN GASTROENTEROLOGY ueg guidelines

Guideline

UNITED EUROPEAN GASTROENTEROLOGY ueg journal

KAROLINSKA INSTITUTET ANNO 1810 · KAROLINSKA UNIVERSITETSSJUKHUSET

European Guideline on IgG4-related digestive disease – UEG and SGF evidence-based recommendations

United European Gastroenterology Journal
2020, Vol. 8(6) 637–666

DOI: 10.1177/2050640620934911
journals.sagepub.com/home/ueg
SAGE

J-Matthias Löhr[1], Ulrich Beuers[2], Miroslav Vujasinovic[3], Domenico Alvaro[4], Jens Brøndum Frøkjær[5], Frank Buttgereit[6], Gabriele Capurso[7], Emma L Culver[8], Enrique de-Madaria[9], Emanuel Della-Torre[10], Sönke Detlefsen[11], Enrique Dominguez-Muñoz[12], Piotr Czubkowski[13], Nils Ewald[14], Luca Frulloni[15], Natalya Gubergrits[16], Deniz Guney Duman[17], Thilo Hackert[18], Julio Iglesias-Garcia[12], Nikolaos Kartalis[19], Andrea Laghi[20], Frank Lammert[21], Fredrik Lindgren[22], Alexey Okhlobystin[23], Grzegorz Oracz[13], Andrea Parniczky[24], Raffaella Maria Pozzi Mucelli[19], Vinciane Rebours[25], Jonas Rosendahl[26], Nicolas Schleinitz[27], Alexander Schneider[28], Eric FH van Bommel[29], Caroline Sophie Verbeke[30], Marie Pierre Vullierme[31], Heiko Witt[32] and the UEG guideline working group[33]

Pancreatology 18 (2018) 900–904

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

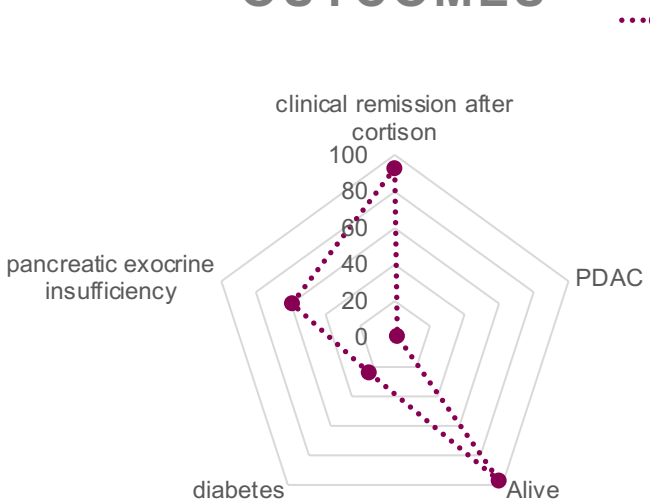
Pancreatic Exocrine Insufficiency in AIP

Diagnosis, treatment and long-term outcome of autoimmune pancreatitis in Sweden

Miroslav Vujasinovic [a], Roberto Valente [a, g], Pia Maier [a], Victoria von Beckerath [a], Stephan L. Haas [a], Urban Arnelo [a], Marco Del Chiaro [a], Nikolaos Kartalis [b, d], Raffaella Maria Pozzi-Mucelli [b, d], Carlos Fernandez-Moro [c], Caroline Sophie Verbeke [c, e], Jingru Yu [f], Weimin Ye [f], J. Matthias Löhr [a, d, *]

Number of patients	71
Male	49%
Mean age	49 years (44-53; 95% CI)
Histologically confirmed	28%
Jaundice	35%
Acute pancreatitis	22%
Non-specific symptoms	39%
Other organ involvement	84%
Radiological features at diagnosis:	
Focal pancreatic enlargement	76%
Diffuse enlargement	27%
Radiological signs of acute pancreatitis	27%
Radiological signs of chronic pancreatitis	10%

SHORT AND LONG TERM OUTCOMES



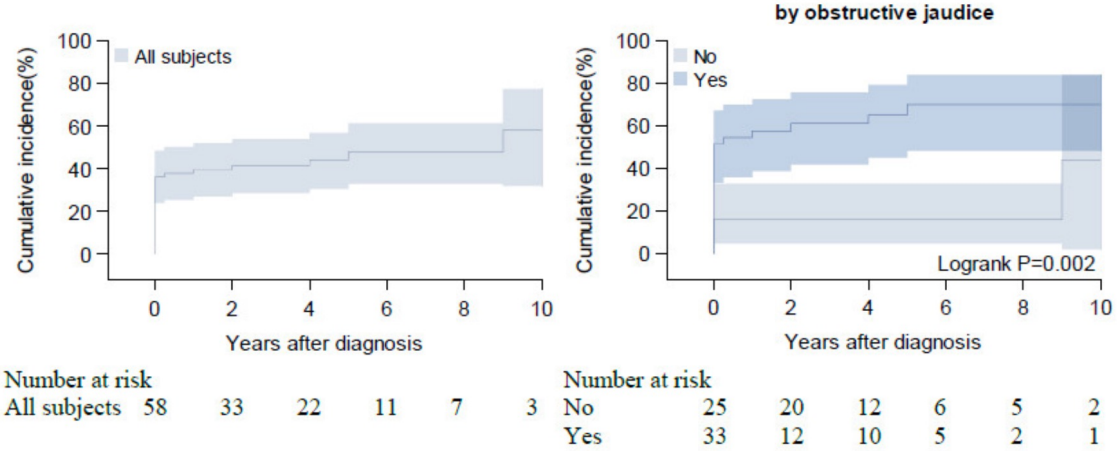
Pancreatic exocrine insufficiency	Type 1 AIP	Type 2 AIP	p = 0.07
	33 (64%)	1 (20%)	

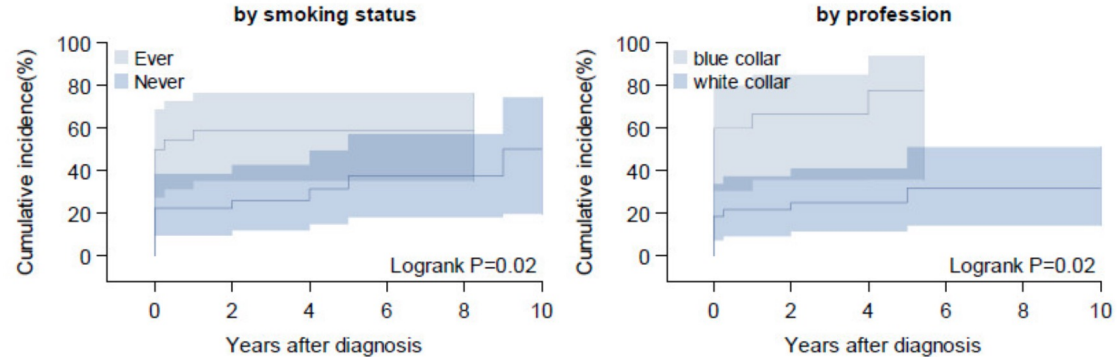
Journal of
Clinical Medicine

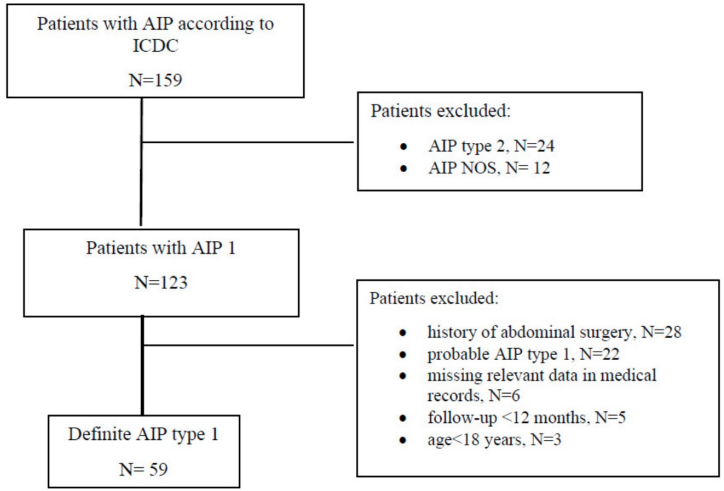
Article

Exocrine and Endocrine Insufficiency in Autoimmune Pancreatitis: A Matter of Treatment or Time?

Sara Nikolic [1,2], Patrick Maisonneuve [3], Ingrid Dahlman [1], J.-Matthias Löhr [4,5,†] and Miroslav Vujasinovic [1,4,*,†]







Journal of Clinical Medicine

Exocrine (PEI) & Endocrine (DM) Insufficiency in AIP

Article

Exocrine and Endocrine Insufficiency in Autoimmune Pancreatitis: A Matter of Treatment or Time?

Sara Nikolic [1,2], Patrick Maisonneuve [3], Ingrid Dahlman [1], J.-Matthias Löhr [4,5,†] and Miroslav Vujasinovic [1,4,*,†]

- PEI prevalence at diagnosis was 72.7%
- The cumulative incidence of DM was 17.9%, with a prevalence of DM at diagnosis of 32.8%.
- No strong association was found between pharmacological treatment and occurrence of PEI and DM.

Author, Year, Country	Patients (N)	Method of PEI Diagnosis	Occurrence of PEI	Occurrence of DM
Frulloni, 2010, Italy [6]	21	FE-1	At AIP diagnosis 62% had severe PEI and 19% mild PEI. After CST, FE-1 levels increased in all patients. Within 1 month after CST, 33% continued to show severe PEI.	Before CST, DM was diagnosed in 5 patients (24%), which increased to 10 patients (48%) during CST. The dosage of insulin was decreased after tapering of steroids and only 4 patients (19%) continued to require low-dose insulin therapy at the end of CST.
Nishino et al., Japan, 2006 [15]	12	BT-PABA	Before CST 6 (67%) of the 9 patients had reduced pancreatic exocrine function. After CST pancreatic exocrine function improved in 3 patients.	10 patients (83.3%) had DM before CST, and in 3 patients HbA1c level improved after the CST. Two patients experienced a transient loss of glycemic control after CST.
Nishimori, 2006, Japan [14]	167	-	Not determined.	66.5% of patients had DM. In the early-onset group 36% showed improvement of DM control, 45% showed no change, and 18% worsening. In the simultaneous-onset group 55% showed improvement of DM control, 29% showed no change, and 16% worsening.
Miyazawa, 2017, Japan [16]	82	-	Not determined.	61.7% of patients had DM. 37.5% showed improvement, 21.9% showed exacerbation, and 40.6% showed no change.
Miyamoto, 2012, Japan [7]	69	BT-PABA	PEI was reduced in 91% of AIP patients with DM. In all patients whose glucose tolerance improved after CST, pancreatic exocrine function also improved.	46% had DM. Three months after starting CST, DM improved in 54% patients. At about 3 years after starting CST, DM improved in 63% of patients.
Kamisawa, 2003, Japan [24]	19	BT-PABA	88% showed reduced pancreatic exocrine function, none of whom reported steatorrhea. Impaired pancreatic exocrine function improved after CST in 3 of 6 patients.	42% with DM. CST subsequently improved insulin secretion and glycaemic control in 3 of 5 patients.
Ito, 2011, Japan [13]	102	BT-PABA	Pancreatic exocrine dysfunction was noted in 74.0% of all patients.	Pre-existing DM-group A (n = 35, 34.3%). New onset DM-group B (n = 58, 56.8%) After steroid therapy (1.5 years)-DM group C (n = 9, 8.8%).
Lee, 2018, South Korea [29]	138	-	Not determined.	45.7% had DM: 28.3% had pre-existing DM, and 17.4% had newly diagnosed DM (simultaneous onset or diagnosis during follow-up).
Noguchi, 2020, Japan [26]	61	-	Not determined.	71% had DM. Anti-diabetic treatment became unnecessary in a quarter of patients with concurrent DM after 2 years of CST. DM was newly diagnosed in 12% of patients without DM at AIP diagnosis during CST.
Masuda, 2014, Japan [27]	31	-	Not determined.	35% had DM. Six months after starting CST, DM was worsening in 9 of 11 DM patients.
Kubota, 2018, Japan [30]	97	-	Not determined.	New-onset DM was noted in 26.2% of patients.
Present study, 2022, Sweden	73	FE-1	Prevalence of PEI at diagnosis: 72.7%. Prevalence of PEI at the last control: 63.5%	The cumulative incidence of DM was 17.9%, with a prevalence of DM at diagnosis of 32.8%.

Exocrine (PEI) & Endocrine (DM) Insufficiency in AIP

Eur J Intern Med. 2022 Mar 30;S0953-6205(22)00104-2. doi: 10.1016/j.ejim.2022.03.014.
Online ahead of print.

Incidence of endocrine and exocrine insufficiency in patients with autoimmune pancreatitis at diagnosis and after treatment: aA systematic review and meta-analysis

Marco Lanzillotta [1], Matteo Tacelli [2], Massimo Falconi [3], Paolo Giorgio Arcidiacono [4], Gabriele Capurso [4], Emanuel Della-Torre [5]

Results: A total of 6522 AIP patients and sixty-two studies were included in the analysis. The pooled estimate rate for the overall prevalence of diabetes in AIP at baseline was 37% (95% CI 32-42, I^2 96%). The pooled prevalence rate of exocrine insufficiency was 45% (95%CI 32.9-57.4; I^2 97%). The pooled estimate rate of diabetes at follow-up was 44% (95%CI 26.1-62.4) in studies where GCs were given to 100% of patients and 42% (95%CI 30.6-52.9) in studies where GCs were given to less than 100% of patients.

Conclusion: A large proportion of patients with AIP displays concomitant exocrine and endocrine insufficiency at the time of diagnosis. The incidence of diabetes at the longest available follow up tends to increase in patients treated with GCs.

45% PEI

Pancreatic atrophy develops fast(er) in AIP

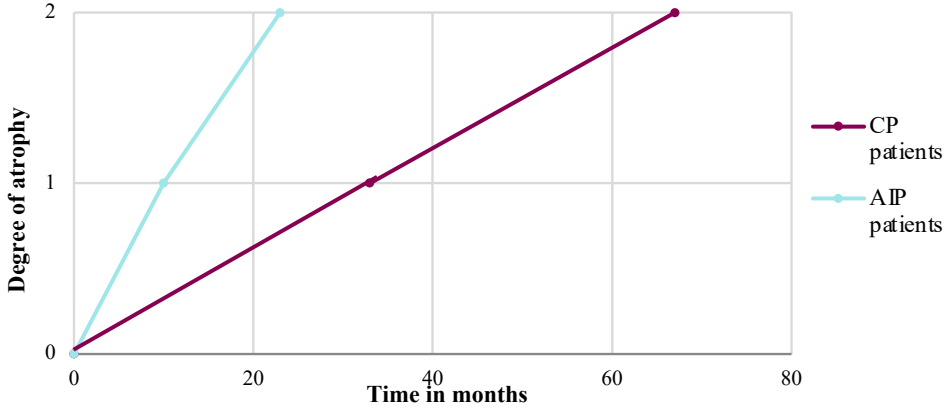


Figure 2: Time to development of **pancreatic atrophy** in patients with **CP** versus **AIP**

- AIP patients develop both pancreatic atrophy and diabetes mellitus ***much faster*** than ordniary chronic pancreatitis

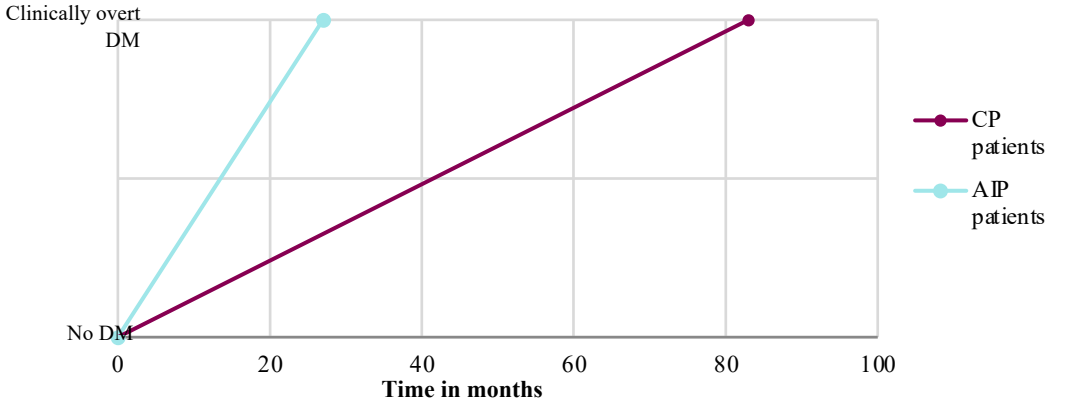


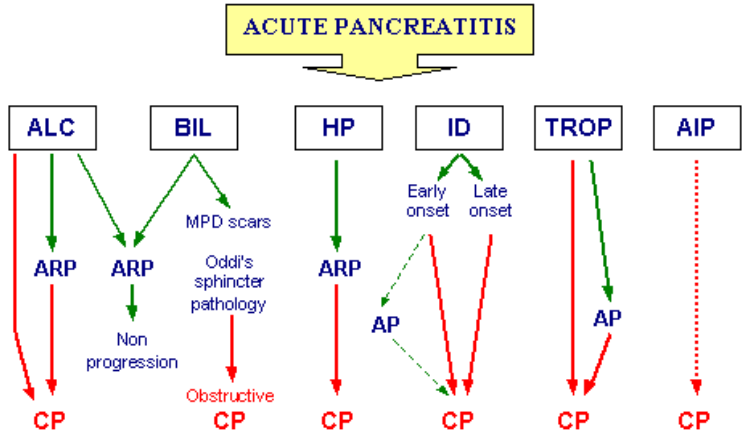
Figure 3: Time to development of clinical overt **diabetes mellitus** in patients with **CP** versus **AIP**

von Beckerath, Vujasinovic, Mucelli-Pozzi, Maisonneuve, Löhr, submitted

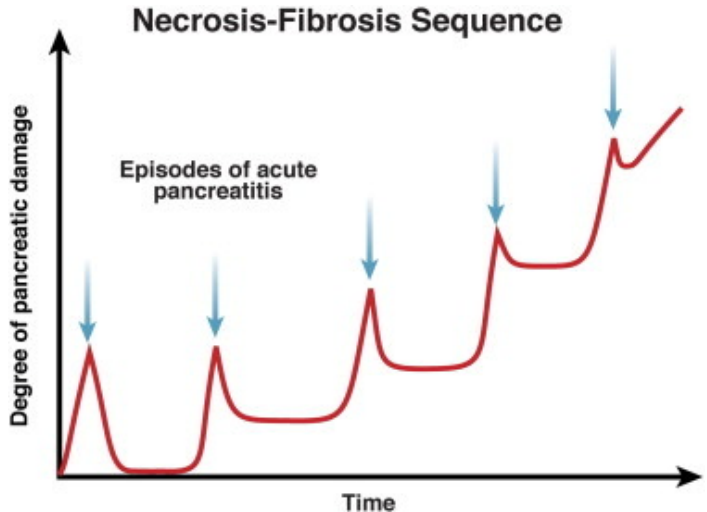
They all come down to CHRONIC PANCREATITIS

- Typically, patients have (had) episodes of
  - →Abdominal pain
  - →Weight loss
  - →Diarrhea

  In the past



- Triggered by
  - →Gallstones
  - →Alcohol
    - Profession!



Cardinal symptoms of chronic pancreatitis - and pancreatic exocrine insufficiency

Diarrhea

EPI can cause problems with undigested food moving too quickly through the digestive tract.

Gas and bloating

People with EPI cannot properly digest the food they eat, which can result in uncomfortable symptoms like gas and bloating.

Stomach pain

Fat maldigestion due to EPI can lead to gas, bloating, and stomach pain.

Foul-smelling, greasy stools (steatorrhea)

Steatorrhea is a type of bowel movement that is oily, floats, smells really bad, and is difficult to flush. People with EPI are not able to absorb all of the fat that they eat, so undigested fat is excreted, resulting in stools that look oily or greasy. Not all people experience this symptom.

Talk to your doctor if you notice oil droplets floating in the toilet bowl or stools that float or stick to the sides of the bowl and are hard to flush; it may be a sign of EPI.

Weight loss

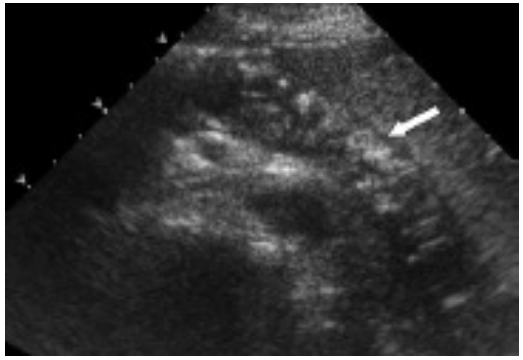
EPI affects protein and carbohydrate digestion, but the greatest impact comes from fat maldigestion, which is the primary cause of weight loss in people with EPI.

- Note: not all symptoms may be present

Othman et al., Clinical Practice 2018

Chronic pancreatitis - Imaging

- While **abdominal ultrasound** is a **good screening** modality in patients with abdominal pain, it is notoriously bad in visualizing the (entire) pancreatic gland.



- Cross-sectional imaging is the method of choice

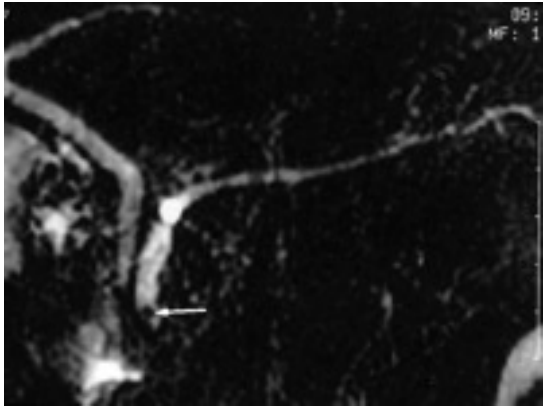
→ CT is the modality with the best

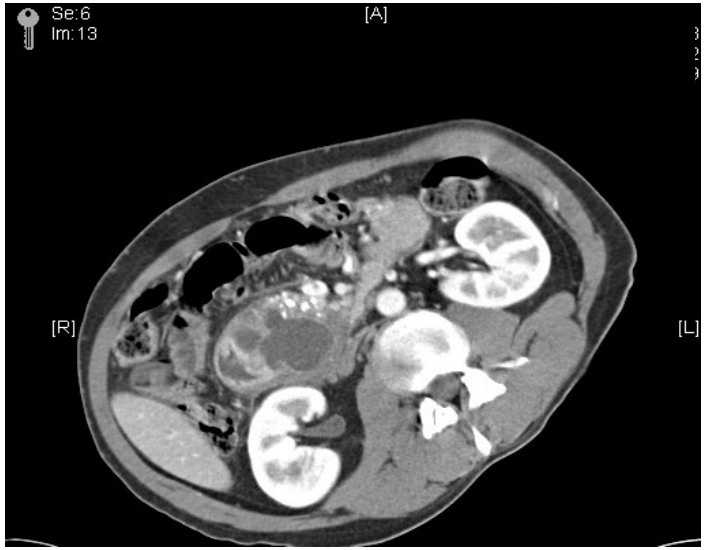
- cost-effectiveness, accessibility, speed
- Diagnostic yield

→ Calcifications & stones

→ MR is next best modality

- With MRCP best for ductal pathology (Cambridge)

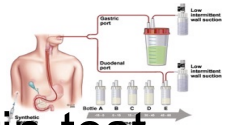




Pancreatic Exocrine Function

Tests

Steatorrhea

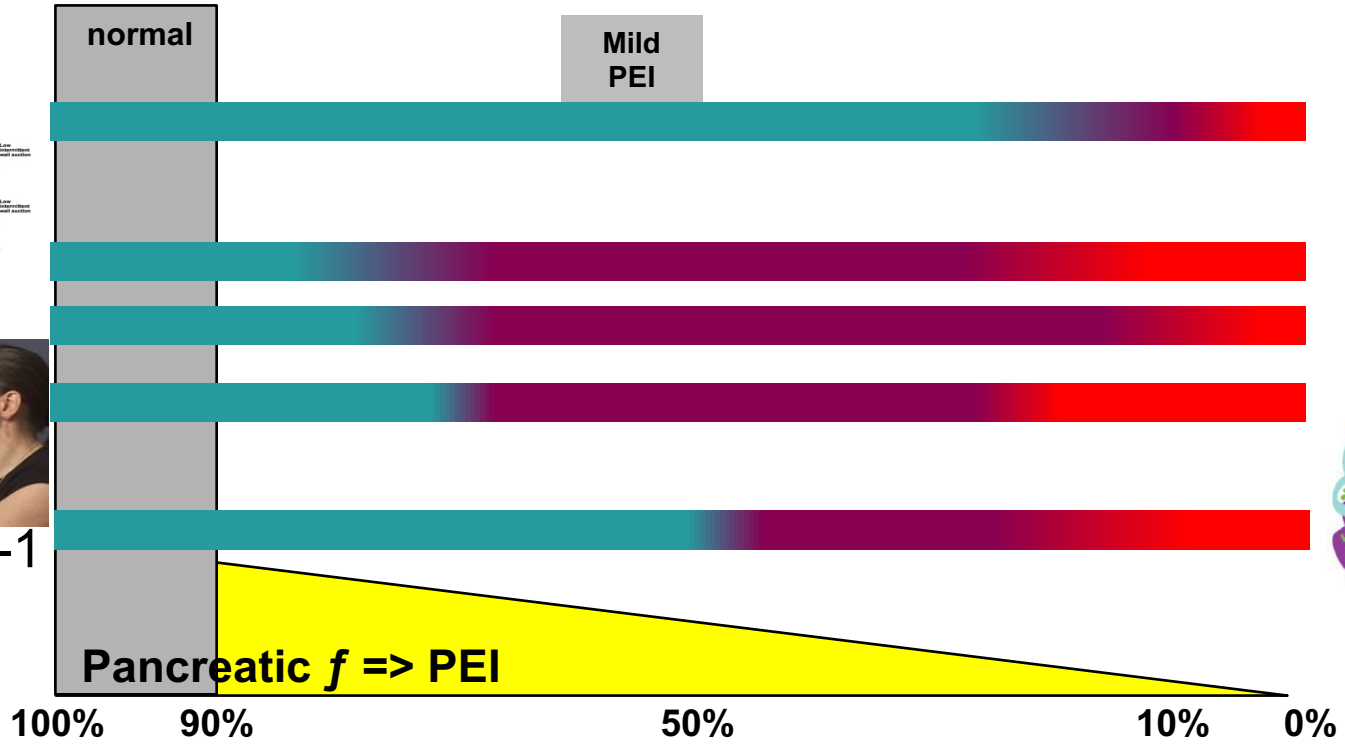


Secretin-test

CFA

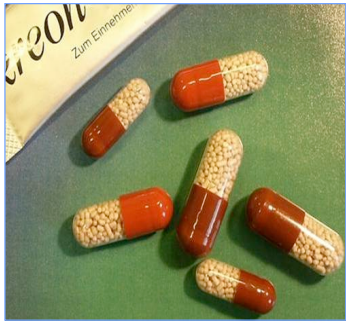
^{13}C-MTG-BT

Fecal elastase-1

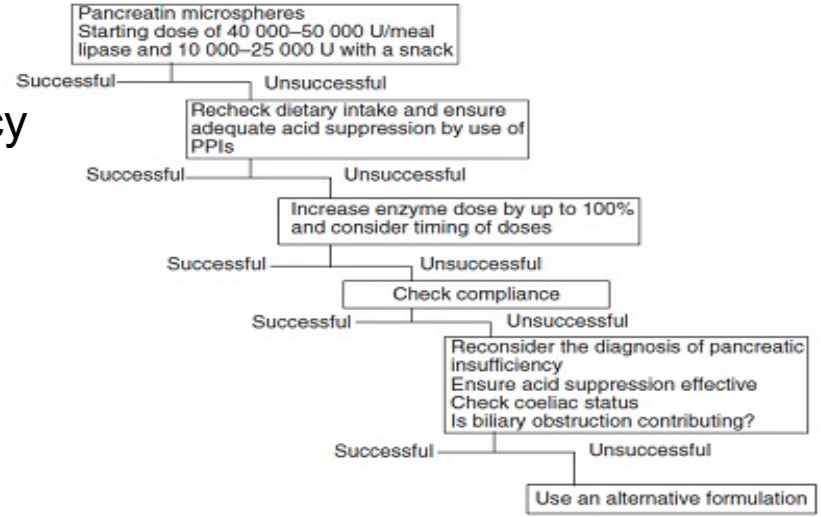


Z Gastroenterol 2004, 42: 1117-1128

Chronic Pancreatitis – Therapy
Pancreatic Enzyme Replacement

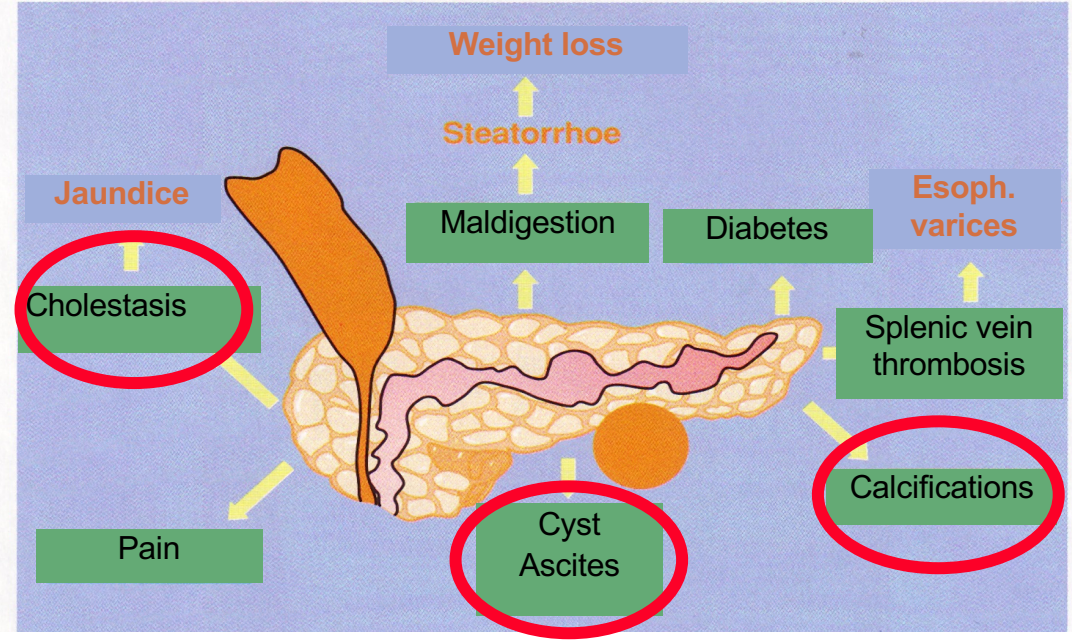


- Indication for PERT
  - →Diagnosed Pancreatic Exocrine Insufficiency
- Adequate starting dose
  - →40-50 k lipase units
- Regular – with all meals
  - →Take during the meals
- Consider individual circumstances
  - →s/p Pancreatic Surgery
  - →Blind/afferent loop
  - →SIBO



uegj 2017, 5: 153-199

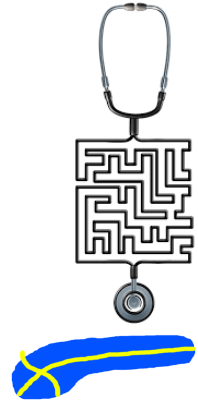
Chronic Pancreatitis - Complications



- Endocrine (diabetes mellitus) and exocrine insufficiency

  →Symptoms/diseases secondary to malnutrition
- Some complications can be treated

  →Surgically or endoscopically O



Pancreatic exocrine insufficiency

Natural Course and Treatment of Pancreatic Exocrine Insufficiency in a Nationwide Cohort of Chronic Pancreatitis

Marinus A. Kempeneers, BSc, Usama Ahmed Ali, MD, PhD,* Yama Issa, MD, PhD,* Harry van Goor, MD, PhD,† Joost P. H. Drenth, MD, PhD,‡ Hendrik M. van Dullemen, MD, PhD,§ Jeanin E. van Hooft, MD, PhD,|| Alexander C. Poen, MD, PhD,¶ Sophie L. van Veldhuisen, MD,* Marc G. Besselink, MD, PhD,* Hjalmar C. van Santvoort, MD, PhD,#** Marco J. Bruno, MD, PhD,†† and Marja A. Boermeester, MD, PhD,* for the Dutch Pancreatitis Study Group*

Pancreas • Volume 49, Number 2, February 2020 *Exocrine Insufficiency in Chronic Pancreatitis*

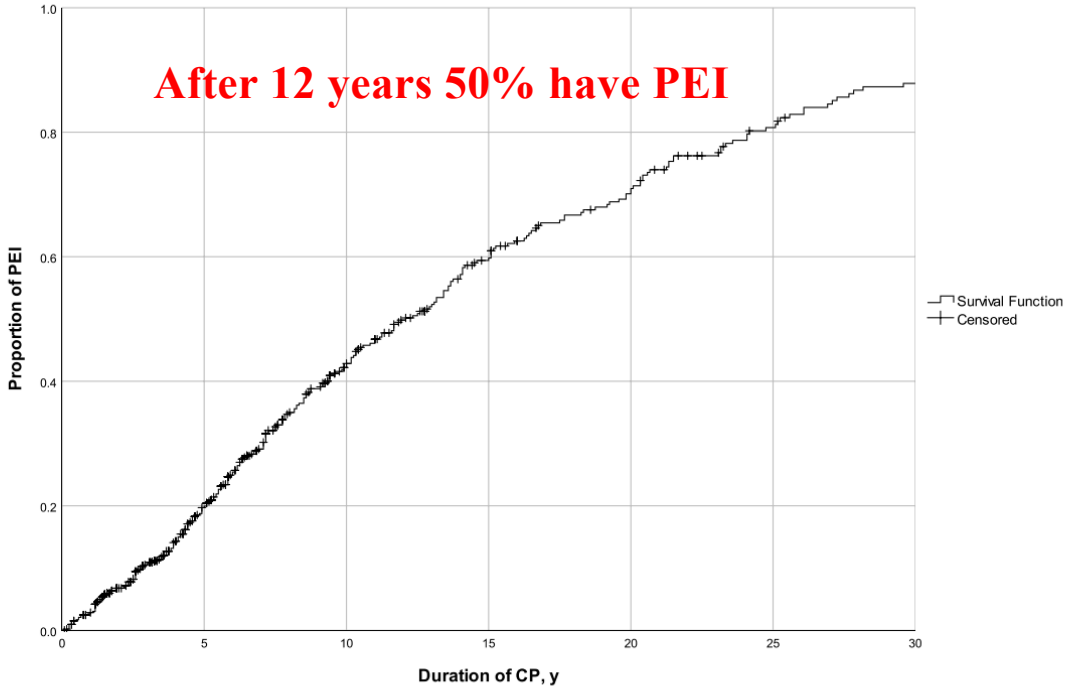


FIGURE 2. Percentage of PEI after the onset of chronic pancreatitis. Correlation between duration CP and percentage PEI shown in a 1 – survival plot.

Kempeneers et al., Pancreas 2020, 49: 242-248

Diabetes mellitus in chronic pancreatitis

Received: 1 August 2022 | Accepted: 20 October 2022
DOI: 10.1002/ueg2.12344

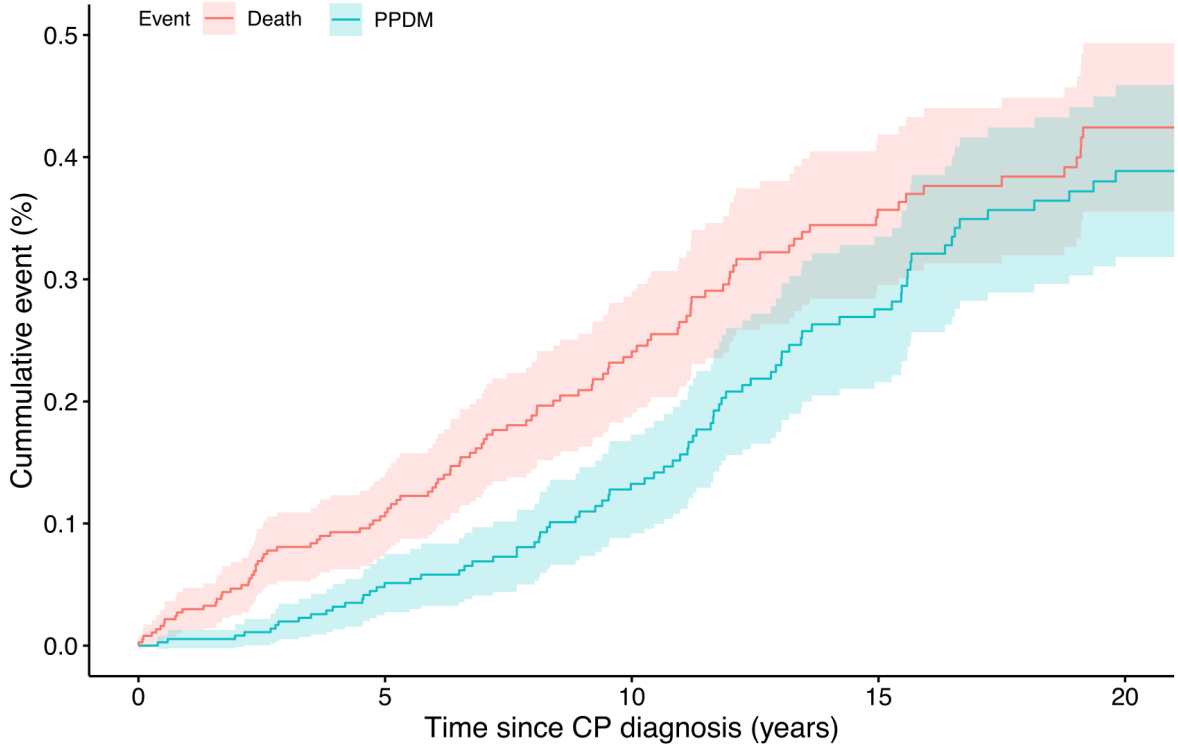
ORIGINAL ARTICLE

ueg journal WILEY

Post-pancreatitis diabetes mellitus is common in chronic pancreatitis and is associated with adverse outcomes

Ana Dugic[1] | Hannes Hagström[1,2,3] | Ingrid Dahlman[1] | Wiktor Rutkowski[1] | Diana Daou[1] | Paula Kulinski[1] | J.-Matthias Löhr[2,4] | Miroslav Vujasinovic[1,2]

- Patients with PPDM have a higher frequency of clinically significant complications and were more commonly prescribed insulin and metformin, suggesting a more aggressive phenotype than that of T2DM



nutrients

MDPI

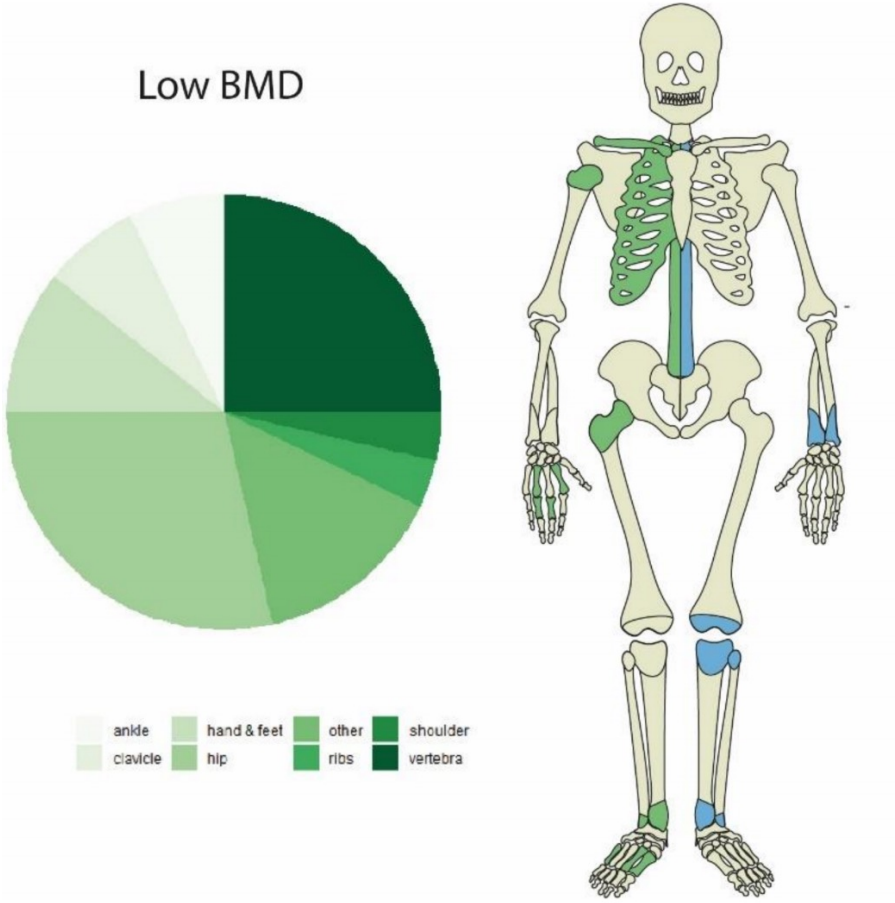
Article

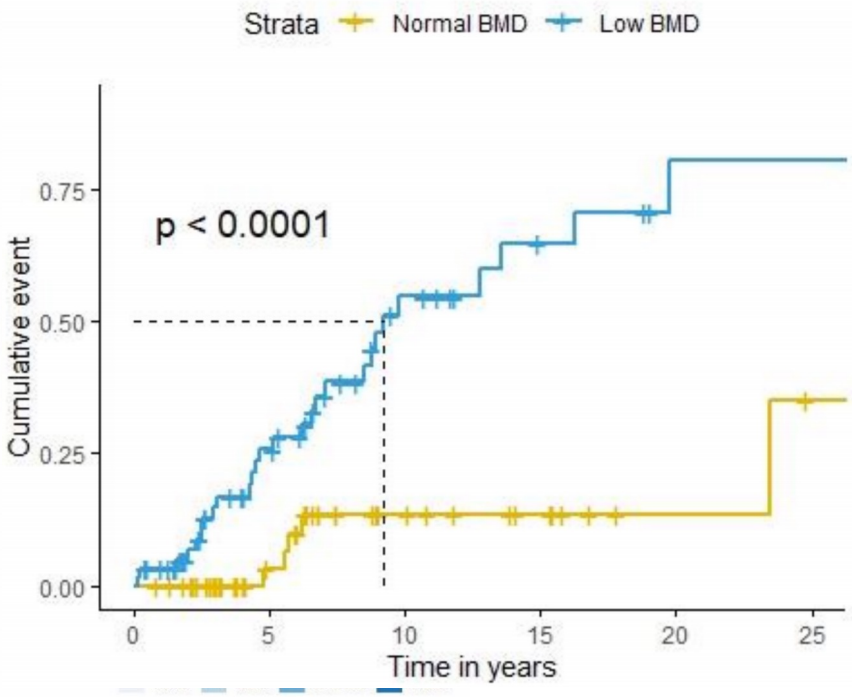
Low Bone Mineral Density and Risk for Osteoporotic Fractures in Patients with Chronic Pancreatitis

Miroslav Vujasinovic [1,2,*], Lorena Nezirevic Dobrijevic [2], Ebba Asplund [2], Wiktor Rutkowski [1,3], Ana Dugic [2], Mashroor Kahn [2], Ingrid Dahlman [2], Maria Sääf [4], Hannes Hagström [1,2,5] and Johannes-Matthias Löhr [1,3]

- 4x fracture rate in low BMD!
- Different fracture pattern
- ⇧ by time

- Consequence
  - DXA-measurent
  - Vitamin D/Ca^{++} treatment





Journal of *Clinical Medicine*

MDPI

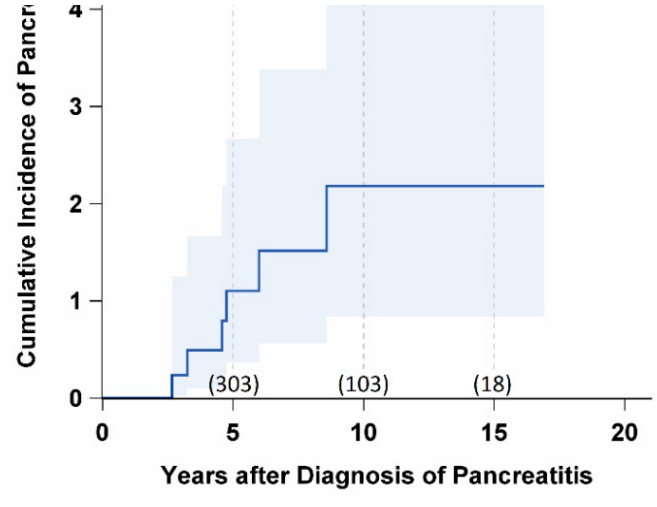
Article

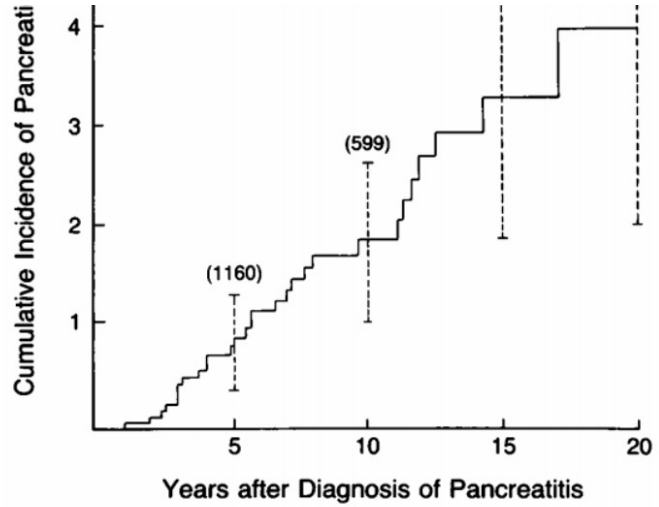
Risk of Developing Pancreatic Cancer in Patients with Chronic Pancreatitis

Miroslav Vujasinovic [1,2,*], Ana Dugic [2], Patrick Maisonneuve [3], Amer Aljic [2], Robin Berggren [2], Nikola Panic [1], Roberto Valente [2], Raffaella Pozzi Mucelli [4,5], Alexander Waldthaler [1,2], Poya Ghorbani [1,4], Maximilian Kordes [1,4], Hannes Hagström [1,2,6] and Johannes-Matthias Löhr [1,4]

Table 3. Pancreas cancer in patients with specific characteristics at diagnosis of CP.

	Patients *N*	Pancreatic Cancers Diagnosed in the First 2 Years after CP * *N* (%)	Pancreas Cancers Diagnosed More than 2 Years after CP *N* (%)	
All	595	14 (2.4)	6 (1.01)	
Risk group				
No previous AP, low BMI, and PEI	22	2 (9.1)	2 (9.1)	
No previous AP, high BMI, and DM	12	2 (16.7)	3 (25.0)	
Other CP patients	561	10 (1.8)	1 (0.18)	$p < 0.001$





10 years: 2% adapted from NEJM **1993**

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United European Gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis (HaPanEU)

United European Gastroenterology Journal
2017, Vol. 5(2) 153–199

DOI: 10.1177/2050640616684695
journals.sagepub.com/home/ueg
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J Matthias Löhr[1], Enrique Dominguez-Munoz[2], Jonas Rosendahl[3], Marc Besselink[4], Julia Mayerle[25], Markus M Lerch[5], Stephan Haas[1], Fatih Akisik[6], Nikolaos Kartalis[7], Julio Iglesias-Garcia[2], Jutta Keller[9], Marja Boermeester[4], Jens Werner[10], Jean-Marc Dumonceau[11], Paul Fockens[4,8], Asbjorn Drewes[12], Gürlap Ceyhan[13], Björn Lindkvist[14], Joost Drenth[15], Nils Ewald[16], Philip Hardt[16], Enrique de Madaria[17], Heiko Witt[18], Alexander Schneider[19], Riccardo Manfredi[20], Frøkjer J Brøndum[21], Sasa Rudolf[22], Thomas Bollen[23] and Marco Bruno[24]; HaPanEU/UEG Working Group

SVENSK GASTROENTEROLOGISK FÖRENING

- Follow-up of all patients AFTER a (first) episode of acute pancreatitis is recommended
  - → Within 6-12 months
    - Take history (pain, weight loss, diarrhea)
    - Measure amylase & lipase
    - Measure endocrine (**HbA1c**) and exocrine (**fecal elastase-1**) function

Svensk Riktlinjer Kronisk Pankreatit

Nya riktlinjer kronisk pankreatit

"Kronisk pankreatit är sannolikt underdiagnostiserad och bör misstänkas vid långvariga högt sittande buksmärtor av oklar genes eller vid tecken till exokrin insufficiens."

I juli publicerades SGFs riktlinjer för Kronisk Pankreatit. I arbetet med dessa har såväl de Europeiska som ett flertal nationella guidelines för kronisk pankreatit samt en mängd originalartiklar beaktats. SGFs riktlinjer baseras således på samma vetenskapliga grund som övriga europeiska riktlinjer, men är anpassade efter svenska förhållanden.

Kronisk pankreatit är sannolikt underdiagnostiserad och bör misstänkas vid långvariga högt sittande buksmärtor av oklar genes eller vid tecken till exokrin insufficiens. Patienter med kronisk pankreatit har en ökad risk för sjuklighet och död. Det är därför viktigt att kunskap om sjukdomen och hur den bör behandlas och följas upp blir tillgänglig.

En sammanfattning av de svenska riktlinjerna publiceras här och de fullständiga riktlinjerna finns på SGFs hemsida http://svenskgastroenterologi.se/wp-content/uploads/2019/07/2018-kronisk-pankreatit.pdf

Definition, Etiologi och Klassifikation

Kronisk pankreatit karakteriseras av en fortgående eller upprepad inflammatorisk process i pankreas, vilken leder till fibrosbildning som medför succesiv förlust av exokrin och endokrin funktion. Processen är irreversibel. Histologiskt ses oregelbundet engagemang av fibros och atrofi av acinära celler samt inflammatoriska infiltrat. Enbart acinär atrofi eller enbart fibros, vilket ibland kan ses hos äldre människor, är inte att betrakta som kronisk pankreatit. Morfologiska förändringar som karakteriserar sjukdomen innefattar oregelbunden utvidgning av gångsystemet, oregelbundet format parenkym med körtelatrofi och något senare förkalkning av gångar och parenkym. Ibland finns lokala komplikationer som t.ex. pseudocystor. I tidiga skeden kan dock morfologiska förändringar saknas. Det finns ingen vedertagen klinisk definition av kronisk pankreatit.

Alkohol är den viktigaste oberoende riskfaktorn för utveckling av kronisk pankreatit. Vanligen uppkommer först akut pankreatit, därefter recidiverande akuta pankreatiter och senare kronisk pankreatit. Rökning är också en oberoende riskfaktor för kronisk pankreatit. Mindre än 5% av patienter med kronisk pankreatit har kända genetiska riskfaktorer. Patienter med mutationer i CFTR, SPINK1, Chymotrypsin C, Carboxypeptidas A generna har förhöjd risk, men utvecklar främst sjukdomen om även andra faktorer finns. Patienter med mutation i katjoniska trypsingenen (PRSS1) har hög risk att utveckla pankreatit redan i barndomen även utan andra riskfaktorer. Dessa patienter har även en hög risk att utveckla pankreascancer.

Det finns olika klassifikationssystem som kategoriserar kronisk pankreatit utifrån etiologi, kliniskt stadium och morfologisk bild. Det finns inget vetenskapligt underlag för att rekommendera vilket klassifikationssystem som bör användas. Någon form av klassificering av sjukdomen utifrån etiologi rekommenderas för alla patienter. M-ANNHEIM eller TIGAR-O klassifikationen kan användas för detta (Tabell 1). Även morfologiska förändringar bör klassificeras.

Klinisk bild och Diagnostik

Kronisk pankreatit bör misstänkas hos patienter med långvariga eller återkommande episoder med högt sittande buksmärtor av oklar genes även om kända episoder av akut pankreatit saknas. Exokrin pankreasinsufficiens med diarre/steatorre, basvärande gaser, viktnedgång och minskad muskelmassa uppträder ofta senare i förloppet. Ungefär 10-20% av patienterna har diabetes när diagnosen kronisk pankreatit ställs, och prevalensen av diabetes ökar när sjukdomen progredierar.

Buksmärtor är ofta det dominerande symtomet, men 10-20% av patienterna rapporterar endast lindriga smärtor eller inga smärtor alls. Typiska smärtor vid kronisk pankreatit beskrivs som molande, krampartade, bandformade över övre delen av buken, ibland strålande bak i ryggen. Det är vanligt att smärtan ökar i samband med måltid. Patienter som diagnosticeras med kronisk pankreatit sent i livet har oftare korta episoder med smärtor (<10 dagar) och långa smärtfria intervaller. Patienter med alkoholrelaterad pankreatit har oftare kroniska smärtor med hög intensitet och korta smärtfria intervaller (<2-3 månader). Det finns inte vetenskapliga belägg som stödjer ett naturalförlopp där smärtorna lindras med tiden eller med tilltagande atrofi av körteln (så kallad "burn out hypotes").

Vid klinisk misstanke om kronisk pankreatit bör bilddiagnostisk undersökning göras för att identifiera morfologiska förändringar.

Transabdominellt ultraljud kan identifiera avancerad kronisk pankreatit, men metoden har ett begränsat värde vid tidiga stadier av sjukdomen. Endoskopiskt ultraljud, MR/MRCP eller datortomografi är relativt likvärdiga för diagnostik av morfologiska förändringar vid kronisk pankreatit. Endoskopiskt ultraljud är bäst på att påvisa tidiga förändringar, och kan även kombineras med finnålsbiopsi vilket ökar den diagnostiska känsligheten. Den rekommenderas dock inte som förstahandsmetod då den är undersökarberoende, invasiv och med varierande tillgänglighet. ERCP var tidigare referensmetod men används i dag enbart vid terapeutisk frågeställning och inte för diagnostik.

Undernäring är vanligt vid kronisk pankreatit. Undernäringen är ofta multifaktoriell och en följd av den inflammatoriska processens påverkan på metabolismen, på minskat energiintag till följd av smärtor och på exokrin pankreasinsufficiens.

Tabell 1

Klassifikation av etiologi/riskfaktorer för kronisk pankreatit enligt TIGAR-O[1] och M-ANNHEIM[2] klassifikationerna (i kortversion och översatt till svenska)

T	Toxisk, metabolisk *(inkluderande alkohol, rökning, hyperkalcemi, kronisk njursvikt)*
I	Idiopatisk *(debut tidigt eller sent i livet)*
G	Genetisk *(PRSS1, CFTR, SPINK mutationer m fl)*
A	Autoimmun
R	Recidiverande eller svår akut pankreatit
O	Obstruktiv *(pankreas divisum, förträngning av gång (sten, tumör, striktur))*
M	Pankreatit med Multipla riskfaktorer
A	Alkohol *(mycket >80g/d, ökat eller moderat intag <20g/d)*
N	Nikotin
N	Nutritionsfaktorer
H	Hereditära faktorer
E	Efferenta faktorer *(pankreas divisum, kongenital pankreasabnormalitet, pankreatisk gångobstruktion, posttraumatiska strikturer)*
I	Immunologisk
M	(Miscellaneaous) Blandat och sällsynt *(hyperkalcemi, kronisk njursvikt, droger, toxin)*

Fritt översatt och förkortat från
1) Etemad B, Whitcomb DC. Chronic pancreatitis: diagnosis, classification, and new genetic developments. Gastroenterology 2001;120:682-707.
2) Schneider A, Löhr JM, Singer MV. The M-ANNHEIM classification of chronic pancreatitis: introduction of a unifying classification system based on a review of previous classifications of the disease. J Gastroenterol 2007;42:101-19.

Vid exokrin pankreasinsufficiens är nivån av pankreasenzymaktivitet i tarmlumen reducerad så att den understiger den som krävs för en normal matsmältning. Försämrad nedbrytning av fett (minskad lipasaktivitet) är den faktor som har störst betydelse för utveckling av symtom och komplikationer. Minskat fettupptag leder dels till steatorré, dels till viktnedgång och dels till nedsatt absorption av fettlösliga vitaminer och mineraler, framför allt vitamin A, D, E och K. En klinisk konsekvens av detta är utveckland av osteoporos.

Om symtom på exokrin insufficiens föreligger och bilddiagnostik talar för kronisk pankreatit kan diagnosen exokrin insufficiens ställas utan ytterligare utredning.

Exokrin pankreasinsufficiens kan dock föreligga utan uppenbara symtom. Fekalt elastas kan användas som screeningtest och bidra till att etablera diagnosen. Nutritionsmarkörer i blod eller tecken till avancerade morfologiska förändringar vid bilddiagnostik kan också stödja diagnosen. ^{13}C triglycerid utandningstest är etablerad i Sverige och kan vara av värde i oklara fall.

Vid misstanke om kronisk pankreatit bör remiss utfärdas till gastroenterolog för utredning och diagnos. Därefter bör majoriteten av patienterna skötas i primärvården.

Behandling och Uppföljning

Alla patienter bör rekommenderas och få hjälp till total avhållsamhet från alkohol och rökning då dessa faktorer bidrar till sjukdomsprogress och ökad risk för komplikationer. Smärtan bör behandlas enligt WHOs riktlinjer. Paracetamol är förstahandsval, medan NSAID bör undvikas främst på grund av risken för gastrointestinala biverkningar. Smärtbehandlingen bör följas upp och mätas utifrån intensitet, mönster och påverkan på dagliga aktiviteter. Då många patienter har missbruksbakgrund är risken för iatrogent opiatmissbruk ökad och samråd med smärtspecialist rekommenderas. Vid förskrivning av opioider bör indikationen utvärderas inom 3 månader.

Om man då inte får acceptabel smärtkontroll utan opioider, trots alkohol- och rökstopp samt adekvat smärtbehandling kan endoskopisk alternativt kirurgisk behandling övervägas. Indikation för pankreaskirurgi bör diskuteras på en multidisciplinär beslutskonferens med en erfaren kirurg och gastroenterolog.

Undernäring och risk för undernäring bör värderas kontinuerligt. Aktuell vikt, viktförlust och åtproblem ska följas och symtom avseende maldigestion specifikt efterfrågas hos patienter med eller utan känd exokrin insufficiens. Det finns inte vetenskapligt underlag för att rekommendera exakta blodprover vid kontroll av patienter med kronisk pankreatit. Baserat på kunskap om sjukdomsförlopp och komplikationer anses det rimligt att utöver rutinprover inkludera leverstatus, amylas, HbA1c och prov som speglar nutritionsstatus, t.ex. vitamin D, zink och prealbumin.

Patienterna bör rekommenderas små måltider som intas ofta. För alla patienter med kronisk pankreatit och samtidiga förekomst av diarre, viktminskning eller andra kliniska eller laborativa tecken på undernäring rekommenderas behandling med pankreasenzymersättningsterapi.

Gastrokuriren 2019, 24: 46-48

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2017, Vol. 5(2) 153–199

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United European Gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis (HaPanEU)

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TREATMENT follows the UNITED EUROPEAN GASTROENTEROLOGY ueg guidelines

The future of HaPanEU

UNITED EUROPEAN GASTROENTEROLOGY ueg guidelines

- Application to UEG for new guidelines - approved
  - →lead specialist society
    - Enrique Dominguez-Munoz, J.-Matthia
  - →Lead National societies
    - Spanish and Swedish Gastro
  - →Supporting spe ieties
    - EDS, ESDO EN, ESPGHAN
  - →Sup ational Societies
    - erman, French, Hungary, Italian, Ukraine

Results presented during ueg week 2023 in Copenhagen!

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United European Gastroenterology Week Copenhagen

Bella Center and Online

October 14–17, 2023

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TACK!


A PRIMER IN PANCREAS
Editors:
J.-Matthias Löhr
Miroslav Vujasinovic