

World Journal of *Clinical Cases*

World J Clin Cases 2021 December 26; 9(36): 11122-11508



REVIEW

- 11122 Diet and microbiome in the beginning of the sequence of gut inflammation
Ceballos D, Hernández-Camba A, Ramos L

MINIREVIEWS

- 11148 Stem cell therapy: A promising treatment for COVID-19
Zheng ZX

ORIGINAL ARTICLE**Case Control Study**

- 11156 Association between serum Sestrin2 level and diabetic peripheral neuropathy in type 2 diabetic patients
Mao EW, Cheng XB, Li WC, Kan CX, Huang N, Wang HS, Hou NN, Sun XD
- 11165 Plasma brain natriuretic peptide, platelet parameters, and cardiopulmonary function in chronic obstructive pulmonary disease
Guo HJ, Jiang F, Chen C, Shi JY, Zhao YW

Retrospective Cohort Study

- 11173 Analysis of the incidence and influencing factors of hyponatremia before ¹³¹I treatment of differentiated thyroid carcinoma
Cao JJ, Yun CH, Xiao J, Liu Y, Wei W, Zhang W

Retrospective Study

- 11183 Cognitive magnetic resonance imaging-ultrasound fusion transperineal targeted biopsy combined with randomized biopsy in detection of prostate cancer
Pang C, Wang M, Hou HM, Liu JY, Zhang ZP, Wang X, Zhang YQ, Li CM, Zhang W, Wang JY, Liu M
- 11193 Nomogram based on inflammation-related markers for predicting survival of patients undergoing hepatectomy for hepatocellular carcinoma
Pu T, Li ZH, Jiang D, Chen JM, Guo Q, Cai M, Chen ZX, Xie K, Zhao YJ, Liu FB
- 11208 Association of frailty with in-hospital outcomes in elderly patients with heart failure
Kang YP, Chen LY, Zhu JJ, Liu WX, Ma CS
- 11220 COVID-19 pandemic and exacerbation of ulcerative colitis
Suda T, Takahashi M, Katayama Y, Tamano M
- 11228 Surgical perspectives of symptomatic omphalomesenteric duct remnants: Differences between infancy and beyond
Kang A, Kim SH, Cho YH, Kim HY

- 11237** Clustering cases of *Chlamydia psittaci* pneumonia mimicking COVID-19 pneumonia
Zhao W, He L, Xie XZ, Liao X, Tong DJ, Wu SJ, Liu J
- 11248** Sodium nitroprusside injection immediately before balloon inflation during percutaneous coronary intervention
Yu Y, Yang BP
- 11255** Machine learning approach to predict acute kidney injury after liver surgery
Dong JF, Xue Q, Chen T, Zhao YY, Fu H, Guo WY, Ji JS
- 11265** Application effect for a care bundle in optimizing nursing of patients with severe craniocerebral injury
Gao Y, Liao LP, Chen P, Wang K, Huang C, Chen Y, Mou SY

Clinical Trials Study

- 11276** Influence of pontic design of anterior fixed dental prosthesis on speech: A clinical case study
Wan J, Cai H, Wang T, Chen JY

Observational Study

- 11285** Real-world data on the infliximab biosimilar CT-P13 (Remsima®) in inflammatory bowel disease
Huguet JM, Cortés X, Bosca-Watts MM, Aguas M, Maroto N, Martí L, Amorós C, Paredes JM
- 11300** Correlation of periodontal inflamed surface area with glycemic status in controlled and uncontrolled type 2 diabetes mellitus
Anil K, Vadakkekuttical RJ, Radhakrishnan C, Parambath FC
- 11311** Audiological characteristics and exploratory treatment of a rare condition of acute-otitis-media-associated sudden sensorineural hearing loss
Cao X, Yi HJ
- 11320** Yield of testing for micronutrient deficiencies associated with pancreatic exocrine insufficiency in a clinical setting: An observational study
Jalal M, Campbell JA, Tesfaye S, Al-Mukhtar A, Hopper AD

Prospective Study

- 11330** Birthing ball on promoting cervical ripening and its influence on the labor process and the neonatal blood gas index
Shen HC, Wang H, Sun B, Jiang LZ, Meng Q

CASE REPORT

- 11338** Mucormycosis – resurgence of a deadly opportunist during COVID-19 pandemic: Four case reports
Upadhyay S, Bharara T, Khandait M, Chawdhry A, Sharma BB
- 11346** Ductal breast carcinoma metastasized to the rectum: A case report and review of the literature
Ban B, Zhang K, Li JN, Liu TJ, Shi J

- 11355** De Garengeot hernia with avascular necrosis of the appendix: A case report
Yao MQ, Yi BH, Yang Y, Weng XQ, Fan JX, Jiang YP
- 11362** Mature mediastinal bronchogenic cyst with left pericardial defect: A case report
Zhu X, Zhang L, Tang Z, Xing FB, Gao X, Chen WB
- 11369** Difficulties in diagnosing anorectal melanoma: A case report and review of the literature
Apostu RC, Stefanescu E, Scurtu RR, Kacso G, Drasovean R
- 11382** Solid pseudopapillary neoplasm of the pancreas in a young male with main pancreatic duct dilatation: A case report
Nakashima S, Sato Y, Imamura T, Hattori D, Tamura T, Koyama R, Sato J, Kobayashi Y, Hashimoto M
- 11392** Acute myocardial infarction in a young man with ankylosing spondylitis: A case report
Wan ZH, Wang J, Zhao Q
- 11400** Acute appendicitis complicated by mesenteric vein thrombosis: A case report
Yang F, Guo XC, Rao XL, Sun L, Xu L
- 11406** Inguinal endometriosis: Ten case reports and review of literature
Li SH, Sun HZ, Li WH, Wang SZ
- 11419** Dramatic response to immunotherapy in an epidermal growth factor receptor-mutant non-small cell lung cancer: A case report
Li D, Cheng C, Song WP, Ni PZ, Zhang WZ, Wu X
- 11425** Three-dimensional inlay-guided endodontics applied in variant root canals: A case report and review of literature
Yan YQ, Wang HL, Liu Y, Zheng TJ, Tang YP, Liu R
- 11437** Ectopic pregnancy implanted under the diaphragm: A rare case report
Wu QL, Wang XM, Tang D
- 11443** Ear ischemia induced by endovascular therapy for arteriovenous fistula of the sigmoid sinus: A case report
Li W, Zhang SS, Gao XR, Li YX, Ge HJ
- 11448** Giant schwannoma of thoracic vertebra: A case report
Zhou Y, Liu CZ, Zhang SY, Wang HY, Varma SN, Cao LQ, Hou TT, Li X, Yao BJ
- 11457** Severe digital ischemia coexists with thrombocytopenia in malignancy-associated antiphospholipid syndrome: A case report and review of literature
Chen JL, Yu X, Luo R, Liu M
- 11467** Rare spontaneous extensive annular intramural esophageal dissection with endoscopic treatment: A case report
Hu JW, Zhao Q, Hu CY, Wu J, Lv XY, Jin XH

- 11475** Mucinous cystic neoplasm of the liver: A case report
Yu TY, Zhang JS, Chen K, Yu AJ
- 11482** Retroperitoneal parasitic fetus: A case report
Xia B, Li DD, Wei HX, Zhang XX, Li RM, Chen J
- 11487** De novo mutation loci and clinical analysis in a child with sodium taurocholate cotransport polypeptide deficiency: A case report
Liu HY, Li M, Li Q
- 11495** Surgery for hepatocellular carcinoma with tumor thrombosis in inferior vena cava: A case report
Zhang ZY, Zhang EL, Zhang BX, Zhang W

LETTER TO THE EDITOR

- 11504** Advantages and issues of concern regarding approaches to peripheral nerve block for total hip arthroplasty
Crisci M, Cuomo A, Forte CA, Bimonte S, Esposito G, Tracey MC, Cascella M

ABOUT COVER

Editorial Board Member of *World Journal of Clinical Cases*, Moises Rodriguez-Gonzalez, MD, Adjunct Professor, Senior Researcher, Department of Pediatric Cardiology, Hospital Universitario Puerta del Mar, Cadiz 11009, Spain. doctormoisesrodriguez@gmail.com

AIMS AND SCOPE

The primary aim of *World Journal of Clinical Cases* (*WJCC*, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

INDEXING/ABSTRACTING

The *WJCC* is now indexed in Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports/Science Edition, Scopus, PubMed, and PubMed Central. The 2021 Edition of Journal Citation Reports® cites the 2020 impact factor (IF) for *WJCC* as 1.337; IF without journal self cites: 1.301; 5-year IF: 1.742; Journal Citation Indicator: 0.33; Ranking: 119 among 169 journals in medicine, general and internal; and Quartile category: Q3. The *WJCC*'s CiteScore for 2020 is 0.8 and Scopus CiteScore rank 2020: General Medicine is 493/793.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Ji-Hong Lin*; Production Department Director: *Xu Guo*; Editorial Office Director: *Jin-Lei Wang*.

NAME OF JOURNAL

World Journal of Clinical Cases

ISSN

ISSN 2307-8960 (online)

LAUNCH DATE

April 16, 2013

FREQUENCY

Thrice Monthly

EDITORS-IN-CHIEF

Bao-Gan Peng

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2307-8960/editorialboard.htm>

PUBLICATION DATE

December 26, 2021

COPYRIGHT

© 2021 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Observational Study

Yield of testing for micronutrient deficiencies associated with pancreatic exocrine insufficiency in a clinical setting: An observational study

Mustafa Jalal, Jennifer Anne Campbell, Solomon Tesfaye, Ahmed Al-Mukhtar, Andrew Derek Hopper

ORCID number: Mustafa Jalal 0000-0002-7498-2743; Jennifer Anne Campbell 0000-0002-3827-5849; Solomon Tesfaye 0000-0003-4219-6753; Ahmed Al-Mukhtar 0000-0002-3010-1975; Andrew Derek Hopper 0000-0001-9530-2703.

Author contributions: Jalal M contributed to study design, data collection, analysis and drafting the manuscript; Campbell JA contributed to data collection, interpretation of data and critically revised the manuscript; Tesfaye S and Al-Mukhtar A contributed to interpretation of data and critically revised the manuscript; Hopper AD contributed to study design, analysis, interpretation of data and critically revised the manuscript; all authors approved the final version of the manuscript.

Institutional review board statement: The study was approved by local research ethics committee (IRAS 210710).

Informed consent statement: Informed consent (STH 19471) was obtained from all patients.

Conflict-of-interest statement: Authors report no conflict of interest.

Mustafa Jalal, Jennifer Anne Campbell, Andrew Derek Hopper, Academic Department of Gastroenterology, Sheffield Teaching Hospitals, Sheffield S10 2JF, United Kingdom

Mustafa Jalal, Department of Infection, Immunology and Cardiovascular disease, University of Sheffield, Sheffield S10 2TN, United Kingdom

Solomon Tesfaye, Academic Unit of Diabetes and Endocrinology, Sheffield Teaching Hospitals, Sheffield S10 2JF, United Kingdom

Ahmed Al-Mukhtar, Department of Surgery, Sheffield Teaching Hospitals, Sheffield S10 2JF, United Kingdom

Corresponding author: Mustafa Jalal, MBChB, MRCP, MSc, Research Fellow, Academic Department of Gastroenterology, Sheffield Teaching Hospitals, Glossop Road, Sheffield S10 2JF, United Kingdom. mustafa.jalal@nhs.net

Abstract

BACKGROUND

Pancreatic exocrine insufficiency (PEI) can be difficult to diagnose and causes maldigestion symptoms and malabsorption. There has been a number of studies that have identified PEI associated micronutrient deficiencies (PEI-MD), however there is variation in both the frequency and type of PEI-MD reported, with the majority of studies including patients with PEI due to chronic pancreatitis (CP) or CP without PEI. There is a paucity of information regarding the prevalence of PEI-MD in patients with PEI without CP and the yield of testing for PEI-MD in a clinical setting in patients with suspected benign pancreatic diseases.

AIM

To prospectively assess the yield and type of PEI-MD in patients with and without PEI secondary to benign pancreatic disease.

METHODS

Patients investigated for maldigestion symptoms with Faecal Elastase-1 (FEL-1) and suspected or proven benign pancreatic disease were prospectively identified. At the time of FEL-1 testing, serum samples were taken for micronutrients identified by previous studies as PEI-MD: prealbumin, retinol binding protein,

Data sharing statement: Data that support the finding of this study are available from corresponding author upon reasonable request.

Country/Territory of origin: United Kingdom

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C

Grade D (Fair): D, D

Grade E (Poor): 0

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Received: August 19, 2021

Peer-review started: August 19, 2021

First decision: October 2, 2021

Revised: October 17, 2021

Accepted: November 14, 2021

Article in press: November 14, 2021

Published online: December 26, 2021

P-Reviewer: Ashihara N, Lakananurak N, Pezzilli R

S-Editor: Wang JL

L-Editor: A

P-Editor: Wang JL



copper, zinc, selenium, magnesium and later in the study lipid adjusted vitamin E. FEL-1 was recorded, with a result < 200 µg/g considered diagnostic of PEI. Patients underwent computed tomography (CT) imaging when there was a clinical suspicion of CP, a new diagnosis of PEI recurrent, pancreatic type pain (epigastric abdominal pain radiating to back with or without previous acute pancreatitis attacks) or weight loss.

RESULTS

After exclusions, 112 patients were recruited that underwent testing for FEL-1 and PEI-MD. PEI was identified in 41/112 (36.6%) patients and a pancreatic CT was performed in 82 patients. Overall a PEI-MD was identified in 21/112 (18.8%) patients. The yield of PEI-MD was 17/41 (41.5%) if PEI was present which was significantly higher than those without 4/71 (5.6%) ($P = 0.0001$). The yield of PEI-MD was significantly higher when PEI and CP were seen together 13/22 (59.1%) compared to CP without PEI and PEI without CP ($P < 0.03$). Individual micronutrient assessment showed a more frequent occurrence of prealbumin 8/41 (19.5%), selenium 6/41 (14.6%) and magnesium 5/41 (12.2%) deficiency when PEI was present (< 0.02). The accuracy of using the significant micronutrients identified in our cohort as a predictor of PEI showed a positive predictive value of 80%-85.7% [95% confidence interval (CI): 38%-100%] and a low sensitivity of 9.8%-19.5% [95% CI: 3.3%-34.9%].

CONCLUSION

Testing for PEI-MD in patients with suspected pancreatic disease has a high yield, specifically when PEI and CP are found together. PEI-MD testing should include selenium, magnesium and prealbumin.

Key Words: Pancreatic exocrine insufficiency; Chronic pancreatitis; Micronutrient; Malnutrition; Malabsorption; Nutritional markers

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Several studies have identified pancreatic exocrine insufficiency associated micronutrient deficiencies (PEI-MD), however, there is a paucity of information for PEI-MD prevalence in patients without chronic pancreatitis (CP) and the yield for testing for these PEI-MD in a clinical setting of suspected benign pancreatic diseases. We performed a clinical based prospective study to determine the yield of testing for PEI-MD when pancreatic exocrine insufficiency (PEI) is present and which specific micronutrients are most beneficial to test. We found high yield of micronutrients deficiency in PEI, in particular when CP was present.

Citation: Jalal M, Campbell JA, Tesfaye S, Al-Mukhtar A, Hopper AD. Yield of testing for micronutrient deficiencies associated with pancreatic exocrine insufficiency in a clinical setting: An observational study. *World J Clin Cases* 2021; 9(36): 11320-11329

URL: <https://www.wjgnet.com/2307-8960/full/v9/i36/11320.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v9.i36.11320>

INTRODUCTION

Pancreatic exocrine insufficiency (PEI) is caused by reduction in the amount of pancreatic enzymes available for digestion in the small intestine[1]. PEI has been shown to cause malabsorption and gastrointestinal symptoms termed 'maldigestion' [2]. A specific concern for PEI is the malabsorption of micronutrients. Micronutrients are essential vitamins and trace elements that are important for normal physiological function, if left untreated, a micronutrient deficiency can cause malnutrition, poor growth, and increased risk of morbidity and mortality[3]. Micronutrient deficiencies can be reversed by treating the underlying condition and by the provision of the deficient micronutrient[3].

There have been a number of studies which aimed to identify individual micronutrient deficiencies associated with PEI. Fat soluble vitamins (vitamin A, E, D) have been a particular focus because lipase is one of most affected enzymes in PEI[4]. An associated incidence of low vitamin A (14.5%-35.2%) and more frequently low vitamin E (17.7%-75%)[5-7] have been reported with vitamin E demonstrating a correlation with faecal fat excretion in one study[8]. Vitamin D is one of the most common markers studied in patients with PEI and chronic pancreatitis (CP) however a sole link to PEI has not been demonstrated. A high prevalence of vitamin D deficiency has been reported in control groups and healthy individuals[5,9]; therefore, vitamin D is not associated with PEI. Along with fat soluble vitamins, trace element and protein deficiencies associated with PEI include prealbumin, retinol-binding protein (RBP), zinc, selenium and magnesium[2,6,8,10,11].

There is variation in both the frequency and type of PEI associated micronutrient deficiency reported, with the majority of studies including patients with PEI due to CP. Micronutrient deficiencies have been identified in patients with CP and PEI but also in CP without PEI[12]. There is increasing evidence that PEI can occur in patients where CP is not the aetiology; there is little information regarding micronutrient deficiency prevalence in this cohort.

The diagnosis of PEI is commonly made using Faecal Elastase-1 (FEL-1) which has grown in acceptance as a less sensitive, but acceptable alternative to direct 'gold standard' tests which can be time-consuming, challenging to tolerate for the patient and difficult to standardize[13]. FEL-1 testing for PEI is recommended in patients with diarrhoea or steatorrhoea, and in primary pancreatic diseases with a high risk of PEI such as CP, cystic fibrosis and other diseases associated with a lower pre-test probability[12,14-17]. It has sensitivity of 63% for mild, and up to 100% for moderate and severe PEI with specificity of 93%[18]. The very high pre-test probability of PEI in pancreatic cancer and the overwhelming benefits of nutritional support has led to guidelines advocating empirical treatment with enzyme replacement without testing with FEL-1[19].

Identification of malnutrition such as PEI associated micronutrient deficiencies (PEI-MD) could improve the accuracy of FEL-1 in mild to moderate PEI and support further testing for PEI in those with normal FEL-1 found to have a micronutrient deficiency.

The primary aim of this study was to prospectively assess the yield of PEI-MD in patients with suspected benign pancreatic diseases. The secondary aim was to assess if micronutrient deficiencies could be used as a tool to test for PEI and prompt further testing in patients with suspected pancreatic pathology.

MATERIALS AND METHODS

Patients referred to our centre with maldigestion symptoms investigated with FEL-1 for suspected or proven benign pancreatic disease were prospectively identified. Patients were excluded if they were aged less than 18 years old, taking pancreatic enzyme replacement therapy (PERT), or had cross-sectional imaging suspicious of pancreatic cancer. At the time of FEL-1, testing PEI associated micronutrient serum levels were obtained for prealbumin, RBP, copper, zinc, selenium, magnesium and later in the study lipid adjusted vitamin E. Vitamin A testing was not available, however as this was a clinical study we indirectly represented this with RBP levels (the carrier for retinol in the blood) which has been shown to predict vitamin A deficiency with a high sensitivity and specificity[20,21]. Serum samples were analysed with standard methods using calibrated ranges. Lipid adjusted Vitamin E was calculated as a ratio of Vitamin E and total cholesterol and triglycerides in a fasting blood sample. Prealbumin and RBP levels were measured by nephelometry.

Demographic information was collected for age, gender, body mass index (BMI), presence of diabetes mellitus (DM), smoking and alcohol intake. FEL-1 was recorded with a result < 200 µg/g considered diagnostic of PEI. A second sample was performed for patients who did not have a FEL-1 result available within the last 3 months or when no cause was identified for a PEI diagnosis. All FEL-1 samples were analysed in our centre with a commercially available enzyme linked immunosorbent assay test which uses two monoclonal antibodies against specific epitopes of human pancreatic elastase (ScheBo-Tech, Wettenberg, Germany).

As part of a clinical pathway patients underwent further investigations including CT imaging when there was a clinical suspicion of CP, a new diagnosis of PEI made on the stool sample, recurrent pancreatic type pain (epigastric abdominal pain radiating to back with or without previous acute pancreatitis attacks) or weight loss[22]. CT

scans of the pancreas were examined for evaluation of CP changes and severity using Cambridge classification[23-25].

Statistical analysis

All results were reported as either a mean with standard deviation or 95% confidence interval for continuous variables. Micronutrients were reported as the number of abnormal low results. Categorical variables were analysed using Fisher's exact test. $P \leq 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS (IBM SPSS statistics version 25, Chicago, Illinois, United States). The study was approved by local research ethics committee (IRAS 210710, STH 19471) and informed consent was obtained from all patients.

RESULTS

Cohort characteristics

After exclusion, 112 patients were recruited that underwent FEL-1 testing and micronutrient assays, as shown in Table 1. PEI was identified in 41 patients and pancreatic imaging was performed in 82 patients. The 30 patients without a CT scan all had FEL-1 > 200, no pancreatic pain symptoms or weight loss and therefore classed as not having CP for analysis. There were 19 patients recruited also that underwent vitamin E assay when it became available.

The aetiology of the 41 patients with PEI was attributed to alcohol-induced chronic pancreatitis ($n = 9$), idiopathic chronic pancreatitis ($n = 4$), pancreatic atrophy ($n = 9$), and when no CP changes or identifiable cause was found, this was termed 'idiopathic PEI', these 19 patients also underwent endoscopic ultrasound (EUS) with no diagnostic criteria for CP reached (range 0-3 EUS features; median 1). Patients with 'idiopathic PEI' were noted to have a history of smoking in 10/19 and alcohol consumption in 11/19 (mean 25.1 ± 28.3 units per week). There was no significant difference in the number of patients with steatorrhoea or weight loss when PEI was present. Ten patients with CP did not have PEI, but CP was felt to be the likely cause of the patients' pain.

The remaining 31 patients who underwent CT for significant symptoms without PEI and no evidence of CP on the CT had a final diagnosis of nonspecific abdominal pain (functional or unexplained) ($n = 14$), biliary dyskinesia ($n = 8$), recent acute pancreatitis with no residual morphological changes ($n = 4$), dyspepsia secondary to gastritis ($n = 3$), and weight loss due to chronic fatigue syndrome ($n = 1$) and consequences of medication from human immunodeficiency virus ($n = 1$).

In total 30 patients that were recruited and tested with FEL-1 without PEI and without the earlier symptoms that did not qualify for a CT scan. The final diagnosis made in patients identified with no PEI and no CT scan was most commonly found to be due to non-specific abdominal pain ($n = 15$), irritable bowel syndrome ($n = 5$), gall stone disease ($n = 4$), or gastritis and peptic ulcer disease ($n = 6$).

Prevalence of micronutrients deficiency

Overall, a micronutrient deficiency was identified in 21/112 (18.8%) patients (Table 2). There were significantly more patients with a micronutrient deficiency when PEI was present 17/41 (41.5%) than those without PEI 4/71 (5.6%) ($P < 0.0001$). Individual micronutrient assessment showed a significantly higher prevalence of prealbumin, selenium and magnesium deficiency when PEI was present.

The micronutrient deficiency occurred as a solitary finding in 16 patients, 2 micronutrient deficiencies in 4 patients and 3 micronutrients deficiencies in one patient.

There was a significantly higher prevalence of patients with a micronutrient deficiency if severe PEI (FEL-1 = 0-100 $\mu\text{g/g}$) was present: 56.5% (13/23), compared to when moderate PEI (FEL-1 = 100-200 $\mu\text{g/g}$) was present: 22.2% (4/18) ($P = 0.05$).

A significantly higher prevalence of patients with a micronutrient deficiency with a low or normal BMI (< 25 kg/m^2): 29.7 % (11/37) was identified compared to a raised BMI (> 25 kg/m^2): 13.3% (10/75) ($P = 0.04$).

As micronutrient levels can vary with inflammation a C-reactive protein (CRP) was also measured in all patients with no significant differences in mean CRP values between patients with PEI (5.6 ± 8.2) and those without PEI (5.1 ± 7.7), or those with a PEI-MD (7.3 ± 10.7) and those without a PEI -MD (4.4 ± 5.4).

Table 1 Demographics of patients with suspected or proven benign pancreatic disease investigated with Faecal Elastase-1 including documented symptoms at time of investigation

	PEI (FEL-1 < 200 µg/g) <i>n</i> = 41, mean ± SD or <i>n</i> (%)	No PEI (FEL-1 > 200 µg/g) <i>n</i> = 71, mean ± SD or <i>n</i> (%)
Age (yr)	58.2 (13.2)	57.4 (5)
Female	14 (34)	44 (61)
BMI (kg/m ²)	26.1 (5.9)	29.9 (7.1)
Type 1 diabetes mellitus	9 (22.0)	11 (15.4)
Type 2 diabetes mellitus	13 (31.7)	26 (36.6)
Alcohol (unit/wk)	17.7 ± (22.9)	12.3 ± (10.5)
Smoking (pack yr)	22.3 ± (21.5)	21.6 ± (20.5)
Morphological changes of CP ¹	22/41 (53.7)	10/41 (24.3)
Clinical symptoms		
Abdominal pain	21	38
Diarrhoea	9	19
Steatorrhoea	2	0
Bloating	5	11
Weight loss	4	3

¹All patients with PEI and 41 patients without PEI but suspected pancreatic disease underwent cross-sectional imaging. PEI: Pancreatic exocrine insufficiency; FEL-1: Faecal elastase-1; CP: Chronic pancreatitis; BMI: Body mass index.

Table 2 Prevalence of micronutrient deficiency¹ in 112 patients with suspected pancreatic disease.

	PEI	No PEI	<i>P</i> value	CP PEI	CP no PEI	PEI no CP	No CP no PEI
<i>n</i> in group	41	71		22	10	19	61
Micronutrients							
Prealbumin	8 (19.5%)	2 (2.8%)	0.005	6 (27.3%)	0	2 (10.5%)	2 (3.2%)
RBP	0	0		0	0	0	0
Selenium	6 (14.6%)	1 (1.4%)	0.01	5 (22.7%)	0	1 (5.3%)	1 (1.6%)
Zinc	0	0		0	0	0	0
Copper	2 (4.9%)	0		1 (4.5%)	0	1 (5.3%)	0
Magnesium	5 (12.2%)	1 (1.4%)	0.02	3 (13.6%)	0	2 (10.5%)	1 (1.6%)
Vitamin E (<i>n</i> = 19)	5/12(41.7%)	1/7 (14.3%)		5/8 (62.5%)	0/5	0/4	1/2(50%)
Total patients with at least 1 deficiency	17(41.5%)	4 (5.6%)	0.0001	13 (59.1%)	0 <i>P</i> = 0.002 ^a	4 (21.1%) <i>P</i> = 0.03 ^b	4 (6.6%)

¹Micronutrient deficiency defined as level below laboratory ranges: Prealbumin 0.2–0.5 g/L; RBP 20–40 mg/L; Copper 11.0–27.2 µmol/L; Zinc 7.2–20.43 µmol/L; Selenium 0.61–1.24 µmol/L; Magnesium 0.7–1.0 mmol/L; Lipid adjusted vitamin E 3.9–5.9 µmol/L.

^aComparing patients with CP and PEI to patients with CP without PEI.

^bComparing patients with CP and PEI to patients with PEI without CP.

PEI: Pancreatic exocrine insufficiency; FEL-1: Faecal Elastase-1; CP: Chronic pancreatitis; RBP: Retinol-binding protein. Grouped according to the presence of PEI (FEL-1 < 200 µg/g) and CP. Significant differences identified are shown if *P* value ≤ 0.05 (Fisher’s test)

Micronutrient deficiency as a prediction of pancreatic enzyme insufficiency

Using the 3-micronutrient deficiencies that were found to have significantly higher deficiency prevalence in patients with PEI (prealbumin, selenium, and magnesium: Table 2) we calculated their accuracy as a test for PEI in our cohort; this showed a positive predictive value of 80%–85.7% and a low sensitivity of 9.8%–19.5% (Table 3).

Table 3 Assessment of significant micronutrient deficiency to predict pancreatic exocrine insufficiency (Faecal Elastase-1 < 200 µg/g)

	Prealbumin	Selenium	Magnesium
Sensitivity	19.5% [95%CI: 8.8-34.9]	14.6% [95%CI: 6.6-33.7]	9.8 % [95%CI: 3.3-21.4]
Specificity	97.2% [95%CI: 90.2-99.7]	98.5% [95%CI: 92.1-99.7]	98.6% [95%CI: 92.4-100]
PPV	80.0% [95%CI: 47.1-94.7]	85.7% [95%CI: 42.1-99.6]	83.3% [95%CI: 37.6-97.7]
NPV	67.7% [95%CI: 64.2-71]	66.7% [95%CI: 56.8-75.6]	60.3% [95%CI: 58.1-62.2]
Accuracy	68.8% [95%CI: 59.3-77.2]	67.9% [95%CI: 58.4-76.3]	61.5% [95%CI: 52.2-70.1]

PPV: Positive predictive value; NPV: Negative predictive value.

DISCUSSION

We have shown in this prospective, clinical based study that specific testing for micronutrients associated with PEI in patients with suspected pancreatic disease has a high yield. The prevalence of micronutrient deficiencies was significantly higher in patients with PEI than those without which confirms the association from previous studies[8,11,26,27]. Micronutrient deficiencies were predominantly higher when PEI and radiological CP changes co-existed. The significant, individual micronutrient deficiencies identified when PEI was present in our study were selenium, magnesium and pre-albumin, and further analysis identified them as a strong predictor of PEI in patients with suspected pancreatic disease. We suggest including selenium, magnesium and pre-albumin when testing for malnutrition in patients with suspected PEI.

The association of the micronutrients that were used in this study with PEI is also strengthened by the increased prevalence of PEI-MD with lower levels of FEL-1 suggesting that malabsorption is a key component. Malabsorption is a possible cause of PEI-MD and this would also be supported by the higher prevalence of micronutrient deficiencies when patients had a low or normal BMI compared to a raised BMI.

The micronutrients chosen to represent PEI-MD in our study were identified from previous studies and clinical availability. Our results are supported by previous studies showing an association of low selenium, magnesium and prealbumin in patients with PEI[11,26,27]. There was variation in our findings for zinc deficiency when compared to other studies with no patients showing a low zinc level. A recent study of 150 patients with CP including 80 with PEI identified a zinc deficiency in 26% with a deficiency significantly associated with age and smoking but not PEI[28]. The absence of zinc deficiency in our CP patients may be in part due to our cohort containing only 28% of patients with CP identified on CT and a lower recommended laboratory cut off for zinc deficiency of 7.2 µmol/L used in our study compared to 11 µmol/L used in this recent study of CP patients[28]. Although we are unable to recommend zinc to be included from our findings, previous studies would suggest testing to have a high yield in CP patients and be included in nutritional assessment in patients with CP. Reanalyzing our data using 11 µmol/L as a cut off would have identified 23 patients with low zinc levels but with a greater proportion in the group without PEI (16/23), therefore not changing the recommendation of our study and reflects the analyser calibration used in our centre.

We only identified 2 patients with a low copper level (both had PEI). The utility of copper as a micronutrient has been studied previously and a high level rather than low level being observed in a cohort of patients with alcohol-induced CP compared to healthy control, reflecting the inflammatory state of CP rather than malabsorption therefore we feel this is unhelpful to be included as a PEI-MD[29].

We detected a significant yield of low prealbumin levels in PEI that has been previously reported, but in the same studies, low RBP levels were also noted in patients with CP[11,30]. We did not detect any low levels of RBP. Both RBP and prealbumin are proteins produced by the liver, pancreas and visceral adipocytes[31, 32]. Increased levels of RBP have been shown to be associated with DM[33,34]. The high prevalence of obesity and DM in our study may explain the absence of RBP deficiency.

We included RBP because vitamin A or retinol was unavailable to the patients in the study and it was felt more appropriate to use RBP in a clinical based or practical study. Retinol is unstable when exposed to heat or light and early studies showed good correlation between concentrations of RBP and retinol[35]. RBP has been shown to

have a reasonable sensitivity and specificity in predicting vitamin A deficiency[20]. RBP has been used as a surrogate marker for vitamin A status which can be a simple, inexpensive tool for assessment of vitamin A deficiency in population studies[21,36], however RBP was unhelpful as a PEI-MD in our study patient group.

We did gain access to a vitamin E testing for patients later in the study with a deficiency noted again in the PEI and CP group; however, the low numbers prevented any significant conclusions. Low fat soluble vitamin E levels would be expected given the reduction of pancreatic lipase secretion[37] and reduced pancreatic bicarbonate secretion, which fails to neutralise the acidic pH in the proximal small bowel causing a further reduction in lipase activity[38]. Most studies assessing vitamin E were in patients with CP with or without PEI[5-8] with a similar picture developing in our cohort. Although vitamin D is a fat-soluble vitamin, we chose not to class it as a PEI-MD as it is not specific to PEI and is significantly prevalent in the general adult population. Although it may be a useful tool to include when assessing general nutritional status, we did not class it as a PEI-MD[5,9]. Fat-soluble vitamins therefore are a major concern in PEI, however in this study their assessment is limited due to our clinical availability of vitamin E (giving lower numbers), vitamin A (using RBP levels as an alternate) and not including those that do not have a significant association (vitamin D), our sample size in this study therefore may have led to it having inadequate power.

We acknowledge that using FEL-1 to diagnose PEI is less accurate compared to 'gold standard' tests, but it widely considered as an acceptable alternative. FEL-1 has become the first line investigation for PEI because it is inexpensive, relatively easy to perform, and readily available. Furthermore, direct 'gold standard' tests can be challenging to patients and staff, time-consuming and expensive[13,39-41]. The limited sensitivity of FEL-1 to detect PEI in mild to moderate PEI[18] could be supported by the high positive predictive value (PPV) and specificity of PEI-MD (selenium, magnesium and prealbumin), therefore, the deficiency of these micronutrients would prompt consideration of retesting or follow up to assess for PEI development in the future. The higher PPV but lower sensitivities of the most significant micronutrients (prealbumin, selenium, and magnesium: Table 2) could be used as a guide in clinical practice to identify those with PEI and who could benefit from PERT. The 4 patients in our study with a micronutrient deficiency but without PEI or CP may be a focus of a further follow up study.

This study used standard laboratory cut off values for micronutrient deficiency in our analysis rather than measuring means. We felt the use of binary reporting (normal or abnormal) is more relevant in clinical practice. We also acknowledge that given the clinical nature of the study a number of patients did not have CT scans performed given the lack of clinical findings and normal FEL-1. These patients were presumed to not have CP; however, it is feasible that we missed patients with radiological changes of CP who were asymptomatic. Changes of CP have been found in up to 12% in post-mortem prevalence studies[42,43]. We did reanalyze the data in patients without CP and no PEI that had a CT (31 of the 71 patients without PEI) as they could have been in a more symptomatic group, but this also showed no new differences or findings.

The strength of our study is the cohort was recruited in a clinical setting according to their symptoms rather than pancreatic morphology. In contrast to previous studies performed exclusively in CP, we were able to include other at-risk groups for PEI including DM. Finding that PEI exists in patients with no radiological features of CP or pancreatic atrophy are not unique. Other work assessing PEI in patients without radiological CP features (on EUS or CT) using FEL-1 reported low values in 5%-32% of patients[44,45]. Using an alternative criteria to look for early CP, the Japanese revised clinical diagnostic criteria for chronic pancreatitis[46], we identified 2 patients from the 19 idiopathic PEI group that would fit the 'early CP' criteria. This was due to the presence of PEI, abdominal pain, raised alcohol intake and 3 EUS features but did not have CP according to the Cambridge criteria used in this study.

The patients without both CP and PEI were in a high-risk group were not a true but comparable control group that would be tested in a clinical setting due to their risk of pancreatic disease.

CONCLUSION

We conclude that micronutrient deficiency, in particular prealbumin, selenium, and magnesium, is common in PEI especially when CP is present. We recommend testing for these markers in those with symptoms suspicious of PEI and pancreatic disease

and consider retesting for PEI if deficiencies occur.

ARTICLE HIGHLIGHTS

Research background

Pancreatic exocrine insufficiency (PEI) can be difficult to diagnose and causes maldigestion symptoms and malabsorption.

Research motivation

There has been a number of studies that have identified PEI associated micronutrient deficiencies (PEI-MD), however there is variation in both the frequency and type of PEI-MD reported with the majority of studies including patients with PEI due to chronic pancreatitis (CP) or CP without PEI.

Research objectives

To prospectively assess the yield and type of PEI-MD in patients with and without PEI secondary to benign pancreatic diseases.

Research methods

Patients investigated for maldigestion symptoms with Faecal Elastase-1 (FEL-1) and suspected or proven benign pancreatic disease were prospectively identified. At the time of FEL-1 testing serum samples were taken for micronutrients identified by previous studies as PEI-MD.

Research results

112 patients were recruited that underwent testing for FEL-1 and PEI-MD. PEI was identified in 41 (36.6%) patients and pancreatic CT was performed in 82 patients. Overall, a PEI-MD was identified in 21/112 (18.8%) patients. The yield of PEI-MD was 17/41 (41.5%) if PEI was present which was significantly higher than those without 4/71 (5.6%) ($P = 0.0001$).

Research conclusions

Testing for PEI-MD in patients with suspected pancreatic disease has a high yield, specifically when PEI and CP are found together.

Research perspectives

We recommend testing for these markers in those with symptoms suspicious of PEI and pancreatic disease and consider retesting for PEI if deficiencies occur. PEI-MD testing should include selenium, magnesium and prealbumin.

REFERENCES

- 1 **Lindkvist B.** Diagnosis and treatment of pancreatic exocrine insufficiency. *World J Gastroenterol* 2013; **19**: 7258-7266 [PMID: 24259956 DOI: 10.3748/wjg.v19.i42.7258]
- 2 **Domínguez-Muñoz JE,** Phillips M. Nutritional Therapy in Chronic Pancreatitis. *Gastroenterol Clin North Am* 2018; **47**: 95-106 [PMID: 29413021 DOI: 10.1016/j.gtc.2017.09.004]
- 3 **Bailey RL,** West KP Jr, Black RE. The epidemiology of global micronutrient deficiencies. *Ann Nutr Metab* 2015; **66**: 22-33 [PMID: 26045325 DOI: 10.1159/000371618]
- 4 **Lippi G,** Valentino M, Cervellin G. Laboratory diagnosis of acute pancreatitis: in search of the Holy Grail. *Crit Rev Clin Lab Sci* 2012; **49**: 18-31 [PMID: 22339380 DOI: 10.3109/10408363.2012.658354]
- 5 **Duggan SN,** Smyth ND, O'Sullivan M, Feehan S, Ridgway PF, Conlon KC. The prevalence of malnutrition and fat-soluble vitamin deficiencies in chronic pancreatitis. *Nutr Clin Pract* 2014; **29**: 348-354 [PMID: 24727205 DOI: 10.1177/0884533614528361]
- 6 **Kalvaria I,** Labadarios D, Shephard GS, Visser L, Marks IN. Biochemical vitamin E deficiency in chronic pancreatitis. *Int J Pancreatol* 1986; **1**: 119-128 [PMID: 3693979 DOI: 10.1007/BF02788444]
- 7 **Min M,** Patel B, Han S, Bocelli L, Kheder J, Vaze A, Wassef W. Exocrine Pancreatic Insufficiency and Malnutrition in Chronic Pancreatitis: Identification, Treatment, and Consequences. *Pancreas* 2018; **47**: 1015-1018 [PMID: 30074926 DOI: 10.1097/MPA.0000000000001137]
- 8 **Nakamura T,** Takebe K, Imamura K, Tando Y, Yamada N, Arai Y, Terada A, Ishii M, Kikuchi H, Suda T. Fat-soluble vitamins in patients with chronic pancreatitis (pancreatic insufficiency). *Acta Gastroenterol Belg* 1996; **59**: 10-14 [PMID: 8686411]

- 9 **Tangpricha V**, Pearce EN, Chen TC, Holick MF. Vitamin D insufficiency among free-living healthy young adults. *Am J Med* 2002; **112**: 659-662 [PMID: [12034416](#) DOI: [10.1016/s0002-9343\(02\)01091-4](#)]
- 10 **Lancellotti L**, D'Orazio C, Mastella G, Mazzi G, Lippi U. Deficiency of vitamins E and A in cystic fibrosis is independent of pancreatic function and current enzyme and vitamin supplementation. *Eur J Pediatr* 1996; **155**: 281-285 [PMID: [8777920](#)]
- 11 **Lindkvist B**, Domínguez-Muñoz JE, Luaces-Regueira M, Castiñeiras-Alvariño M, Nieto-García L, Iglesias-García J. Serum nutritional markers for prediction of pancreatic exocrine insufficiency in chronic pancreatitis. *Pancreatol* 2012; **12**: 305-310 [PMID: [22898630](#) DOI: [10.1016/j.pan.2012.04.006](#)]
- 12 **Price DA**, Schmid ML, Ong EL, Adjukiewicz KM, Peaston B, Snow MH. Pancreatic exocrine insufficiency in HIV-positive patients. *HIV Med* 2005; **6**: 33-36 [PMID: [15670250](#) DOI: [10.1111/j.1468-1293.2005.00263.x](#)]
- 13 **Siegmund E**, Löhr JM, Schuff-Werner P. The diagnostic validity of non-invasive pancreatic function tests--a meta-analysis. *Z Gastroenterol* 2004; **42**: 1117-1128 [PMID: [15508057](#) DOI: [10.1055/s-2004-813604](#)]
- 14 **Maconi G**, Dominici R, Molteni M, Ardizzone S, Bosani M, Ferrara E, Gallus S, Panteghini M, Porro GB. Prevalence of pancreatic insufficiency in inflammatory bowel diseases. Assessment by fecal elastase-1. *Digestive Diseases and Sciences* 2008; **53**: 262-270 [DOI: [10.1007/s10620-007-9852-y](#)]
- 15 **Mohapatra S**, Majumder S, Smyrk TC, Zhang L, Matveyenko A, Kudva YC, Chari ST. Diabetes Mellitus Is Associated With an Exocrine Pancreatopathy: Conclusions From a Review of Literature. *Pancreas* 2016; **45**: 1104-1110 [PMID: [26918874](#) DOI: [10.1097/MPA.0000000000000609](#)]
- 16 **Hardt PD**, Hauenschild A, Nalop J, Marzeion AM, Jaeger C, Teichmann J, Bretzel RG, Hollenhorst M, Kloer HU, Grp SSS. High prevalence of exocrine pancreatic insufficiency in diabetes mellitus-A multicenter study screening fecal elastase 1 concentrations in 1,021 diabetic patients. *Pancreatol* 2003; **3**: 395-402 [DOI: [10.1159/000073655](#)]
- 17 **Leeds JS**, Hopper AD, Sidhu R, Simonette A, Azadbakht N, Hoggard N, Morley S, Sanders DS. Some Patients With Irritable Bowel Syndrome May Have Exocrine Pancreatic Insufficiency. *Clinical Gastroenterology and Hepatology* 2010; **8**: 433-438 [DOI: [10.1016/j.cgh.2009.09.032](#)]
- 18 **Löser C**, Möllgaard A, Fölsch UR. Faecal elastase 1: a novel, highly sensitive, and specific tubeless pancreatic function test. *Gut* 1996; **39**: 580-586 [PMID: [8944569](#)]
- 19 **Smith RC**, Smith SF, Wilson J, Pearce C, Wray N, Vo R, Chen J, Ooi CY, Oliver M, Katz T, Turner R, Nikfarjam M, Rayner C, Horowitz M, Holtmann G, Talley N, Windsor J, Pirola R, Neale R. Summary and recommendations from the Australasian guidelines for the management of pancreatic exocrine insufficiency. *Pancreatol* 2016; **16**: 164-180 [PMID: [26775768](#) DOI: [10.1016/j.pan.2015.12.006](#)]
- 20 **Almekinder J**, Manda W, Soko D, Lan Y, Hoover DR, Semba RD. Evaluation of plasma retinol-binding protein as a surrogate measure for plasma retinol concentrations. *Scand J Clin Lab Invest* 2000; **60**: 199-203 [PMID: [10885491](#) DOI: [10.1080/003655100750044848](#)]
- 21 **Baeten JM**, Richardson BA, Bankson DD, Wener MH, Kreiss JK, Lavreys L, Mandaliya K, Bwayo JJ, McClelland RS. Use of serum retinol-binding protein for prediction of vitamin A deficiency: effects of HIV-1 infection, protein malnutrition, and the acute phase response. *Am J Clin Nutr* 2004; **79**: 218-225 [PMID: [14749226](#) DOI: [10.1093/ajcn/79.2.218](#)]
- 22 **Conwell DL**, Lee LS, Yadav D, Longnecker DS, Miller FH, Mortele KJ, Levy MJ, Kwon R, Lieb JG, Stevens T, Toskes PP, Gardner TB, Gelrud A, Wu BU, Forsmark CE, Vege SS. American Pancreatic Association Practice Guidelines in Chronic Pancreatitis Evidence-Based Report on Diagnostic Guidelines. *Pancreas* 2014; **43**: 1143-1162
- 23 **Catalano MF**, Sahai A, Levy M, Romagnuolo J, Wiersema M, Brugge W, Freeman M, Yamao K, Canto M, Hernandez LV. EUS-based criteria for the diagnosis of chronic pancreatitis: the Rosemont classification. *Gastrointest Endosc* 2009; **69**: 1251-1261 [PMID: [19243769](#) DOI: [10.1016/j.gie.2008.07.043](#)]
- 24 **Sarner M**, Cotton PB. CLASSIFICATION OF PANCREATITIS. *Gut* 1984; **25**: 756-759 [DOI: [10.1136/gut.25.7.756](#)]
- 25 **Singer MV**, Lohr MJ, Schneider A. The M-ANNHEIM classification of chronic pancreatitis: a unifying classification system based on a review of previous classifications of the disease. *Journal of Gastroenterology and Hepatology* 2007; **22**: A144-A144
- 26 **Sobral-Oliveira MB**, Faintuch J, Guarita DR, Oliveira CP, Carrilho FJ. Nutritional profile of asymptomatic alcoholic patients. *Arq Gastroenterol* 2011; **48**: 112-118 [PMID: [21709952](#) DOI: [10.1590/s0004-28032011000200006](#)]
- 27 **Vaona B**, Stanzial AM, Talamini G, Bovo P, Corrocher R, Cavallini G. Serum selenium concentrations in chronic pancreatitis and controls. *Dig Liver Dis* 2005; **37**: 522-525 [PMID: [15975540](#) DOI: [10.1016/j.dld.2005.01.013](#)]
- 28 **Vujasinovic M**, Hedström A, Maisonneuve P, Valente R, von Horn H, Löhr JM, Haas SL. Zinc deficiency in patients with chronic pancreatitis. *World J Gastroenterol* 2019; **25**: 600-607 [PMID: [30774274](#) DOI: [10.3748/wjg.v25.i5.600](#)]
- 29 **Van Gossum A**, Closset P, Noel E, Cremer M, Neve J. Deficiency in antioxidant factors in patients with alcohol-related chronic pancreatitis. *Dig Dis Sci* 1996; **41**: 1225-1231 [PMID: [8654156](#) DOI: [10.1007/BF02088241](#)]
- 30 **Laszity N**, Biro L, Nemeth E, Pap A, Antal M. Protein status in pancreatitis-transthyretin is a

- sensitive biomarker of malnutrition in acute and chronic pancreatitis. *Clin Chem Lab Med* 2002; **40**: 1320-1324 [PMID: [12553437](#) DOI: [10.1515/CCLM.2002.227](#)]
- 31 **Pullakhandam R**, Palika R, Ghosh S, Reddy GB. Contrasting effects of type 2 and type 1 diabetes on plasma RBP4 levels: the significance of transthyretin. *IUBMB Life* 2012; **64**: 975-982 [PMID: [23129325](#) DOI: [10.1002/iub.1096](#)]
- 32 **Klötting N**, Graham TE, Berndt J, Kralisch S, Kovacs P, Wason CJ, Fasshauer M, Schön MR, Stumvoll M, Blüher M, Kahn BB. Serum retinol-binding protein is more highly expressed in visceral than in subcutaneous adipose tissue and is a marker of intra-abdominal fat mass. *Cell Metab* 2007; **6**: 79-87 [PMID: [17618858](#) DOI: [10.1016/j.cmet.2007.06.002](#)]
- 33 **Cho YM**, Youn BS, Lee H, Lee N, Min SS, Kwak SH, Lee HK, Park KS. Plasma retinol-binding protein-4 concentrations are elevated in human subjects with impaired glucose tolerance and type 2 diabetes. *Diabetes Care* 2006; **29**: 2457-2461 [PMID: [17065684](#) DOI: [10.2337/dc06-0360](#)]
- 34 **Takebayashi K**, Suetsugu M, Wakabayashi S, Aso Y, Inukai T. Retinol binding protein-4 levels and clinical features of type 2 diabetes patients. *J Clin Endocrinol Metab* 2007; **92**: 2712-2719 [PMID: [17440021](#) DOI: [10.1210/jc.2006-1249](#)]
- 35 **Smith FR**, Goodman DS, Arroyave G, Viteri F. Serum vitamin A, retinol-binding protein, and prealbumin concentrations in protein-calorie malnutrition. II. Treatment including supplemental vitamin A. *Am J Clin Nutr* 1973; **26**: 982-987 [PMID: [4199433](#) DOI: [10.1093/ajcn/26.9.982](#)]
- 36 **Chaves GV**, Peres WA, Gonçalves JC, Ramalho A. Vitamin A and retinol-binding protein deficiency among chronic liver disease patients. *Nutrition* 2015; **31**: 664-668 [PMID: [25837210](#) DOI: [10.1016/j.nut.2014.10.016](#)]
- 37 **Layer P**, Go VL, DiMagno EP. Fate of pancreatic enzymes during small intestinal aboral transit in humans. *Am J Physiol* 1986; **251**: G475-G480 [PMID: [2429560](#) DOI: [10.1152/ajpgi.1986.251.4.G475](#)]
- 38 **Vuoristo M**, Väänänen H, Miettinen TA. Cholesterol malabsorption in pancreatic insufficiency: effects of enzyme substitution. *Gastroenterology* 1992; **102**: 647-655 [PMID: [1732134](#) DOI: [10.1016/0016-5085\(92\)90115-f](#)]
- 39 **Hill PG**. Faecal fat: time to give it up. *Ann Clin Biochem* 2001; **38**: 164-167 [PMID: [11392492](#) DOI: [10.1258/0004563011900605](#)]
- 40 **Burton P**, Evans DG, Harper AA, Howath T, Oleesky S, Scott JE, Varley H. A test of pancreatic function in man based on the analysis of duodenal contents after administration of secretin and pancreozymin. *Gut* 1960; **1**: 111-124 [PMID: [13806339](#) DOI: [10.1136/gut.1.2.111](#)]
- 41 **Stevens T**, Conwell DL, Zuccaro G Jr, Van Lente F, Lopez R, Purich E, Fein S. A prospective crossover study comparing secretin-stimulated endoscopic and Dreiling tube pancreatic function testing in patients evaluated for chronic pancreatitis. *Gastrointest Endosc* 2008; **67**: 458-466 [PMID: [18294508](#) DOI: [10.1016/j.gie.2007.07.028](#)]
- 42 **Olsen TS**. Incidence and clinical relevance of chronic inflammation in pancreas in autopsy material. *Acta Pathologica Et Microbiologica Scandinavica Section a-Pathology* 1978; **86**: 361-365
- 43 **Blumenthal HT**, Probst JG, Berns AW. Interrelationship of diabetes mellitus and pancreatitis. *Archives of Surgery* 1963; **87**: 844-850
- 44 **Shobassy M**, Husainat N, Tabash A, Patel K, El-Serag HB, Othman MO. Endoscopic Ultrasound Findings in Patients Diagnosed with Exocrine Pancreatic Insufficiency by Low Fecal Elastase-1. *Gastroenterol Res Pract* 2019; **2019**: 5290642 [PMID: [31485218](#) DOI: [10.1155/2019/5290642](#)]
- 45 **Bilgin M**, Balci NC, Momtahan AJ, Bilgin Y, Klor HU, Rau WS. MRI and MRCP Findings of the Pancreas in Patients With Diabetes Mellitus Compared Analysis With Pancreatic Exocrine Function Determined by Fecal Elastase 1. *Journal of Clinical Gastroenterology* 2009; **43**: 165-170
- 46 **Shimosegawa T**, Kataoka K, Kamisawa T, Miyakawa H, Ohara H, Ito T, Naruse S, Sata N, Suda K, Hirota M, Takeyama Y, Shiratori K, Hatori T, Otsuki M, Atomi Y, Sugano K, Tanaka M. The revised Japanese clinical diagnostic criteria for chronic pancreatitis. *J Gastroenterol* 2010; **45**: 584-591 [PMID: [20422433](#) DOI: [10.1007/s00535-010-0242-4](#)]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: bpgoffice@wjgnet.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

