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Contents

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MINIREVIEWS

6483 Inositol 1,4,5-trisphosphate receptor in the liver: Expression and function
Lemos FDO, Florentino RM, Lima Filho ACM, Santos MLD, Leite MF

ORIGINAL ARTICLE

Basic Study

6495 Reduced microRNA 375 in colorectal cancer upregulates metadherin-mediated signaling
Han SH, Mo JS, Park WC, Chae SC

6508 Long noncoding RNA NALT1-induced gastric cancer invasion and metastasis *via* NOTCH signaling pathway
Piao HY, Guo S, Wang Y, Zhang J

6527 Gasdermin D-mediated hepatocyte pyroptosis expands inflammatory responses that aggravate acute liver failure by upregulating monocyte chemotactic protein 1/CC chemokine receptor-2 to recruit macrophages
Li H, Zhao XK, Cheng YJ, Zhang Q, Wu J, Lu S, Zhang W, Liu Y, Zhou MY, Wang Y, Yang J, Cheng ML

Retrospective Study

6541 Cystic duct cancer: Should it be deemed as a type of gallbladder cancer?
Yu TN, Mao YY, Wei FQ, Liu H

Observational Study

6551 Real life efficacy and safety of direct-acting antiviral therapy for treatment of patients infected with hepatitis C virus genotypes 1, 2 and 3 in northwest China
Yang Y, Wu FP, Wang WJ, Shi JJ, Li YP, Zhang X, Dang SS

SYSTEMATIC REVIEW

6561 Chronic pancreatitis and the heart disease: Still terra incognita?
Nikolic S, Dugic A, Steiner C, Tsolakis AV, Haugen Löfman IM, Löhr JM, Vujasinovic M

CASE REPORT

6571 Primary gastric melanoma: A case report with imaging findings and 5-year follow-up
Wang J, Yang F, Ao WQ, Liu C, Zhang WM, Xu FY

Contents

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Volume 25 Number 44 November 28, 2019

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SYSTEMATIC REVIEW

Chronic pancreatitis and the heart disease: Still terra incognita?

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Abstract

BACKGROUND

It has been suggested that chronic pancreatitis (CP) may be an independent risk factor for development of cardiovascular disease (CVD). At the same time, it seems that congestive heart failure (CHF) and CP share the responsibility for the development of important clinical conditions such as sarcopenia, cachexia and malnutrition due to development of cardiac cachexia and pancreatic exocrine insufficiency (PEI), respectively.

AIM

To explore the evidence regarding the association of CP and heart disease, more specifically CVD and CHF.

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METHODS
A systematic search of MEDLINE, Web of Science and Google Scholar was performed by two independent investigators to identify eligible studies where the connection between CP and CVD was investigated. The search was limited to articles in the English language. The last search was run on the 1st of May 2019. The primary outcomes were: (1) Incidence of cardiovascular event [acute coronary syndrome (ACS), chronic coronary disease, peripheral arterial lesions] in patients with established CP; and (2) Incidence of PEI in patients with CHF.

RESULTS
Out of 1166 studies, only 8 were eligible for this review. Studies regarding PEI and CHF showed an important incidence of PEI as well as associated malabsorption of nutritional markers (vitamin D, selenium, phosphorus, zinc, folic acid, and prealbumin) in patients with CHF. However, after substitution of pancreatic enzymes, it seems that, at least, loss of appetite was attenuated. On the other side, studies investigating cardiovascular events in patients with CP showed that, in CP cohort, there was a 2.5-fold higher incidence of ACS. In another study, patients with alcohol–induced CP with concomitant type 3c diabetes had statistically significant higher incidence of carotid atherosclerotic plaques in comparison to patients with diabetes mellitus of other etiologies. Earlier studies demonstrated a marked correlation between the clinical symptoms in CP and chronic coronary insufficiency. Also, statistically significant higher incidence of arterial lesions was found in patients with CP compared to the control group with the same risk factors for atherosclerosis (hypertension, smoking, dyslipidemia). Moreover, one recent study showed that PEI is significantly associated with the risk of cardiovascular events in patients with CP.

CONCLUSION
Current evidence implicates a possible association between PEI and malnutrition in patients with CHF. Chronic pancreatic tissue hypoxic injury driven by prolonged splanchnic hypoperfusion is likely to contribute to malnutrition and cachexia in patients with CHF. On the other hand, CP and PEI seem to be an independent risk factor associated with an increased risk of cardiovascular events.

Key words: Chronic; Pancreatitis; Pancreatic exocrine insufficiency; Heart failure; Cardiovascular diseases

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Core tip: This systematic review explores the studies regarding the connection between chronic pancreatitis (CP) and cardiovascular disease, which seems to be a two-way street. On one hand, congestive heart failure may aid to development of at least mild pancreatic exocrine insufficiency (PEI) that, in return, contributes to development of loss of appetite, cachexia, and malnutrition in patients with heart failure. On the other hand, there is some evidence that CP with concomitant PEI may be an independent risk factor for cardiovascular events in terms of coronary disease, cerebrovascular disease and peripheral atherosclerotic plaques.

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INTRODUCTION

Chronic pancreatitis (CP) is a persistent inflammation of the pancreas with pathological findings of the infiltration of immune cells and the development of fibrosis. Pancreatic exocrine insufficiency (PEI), caused by impaired secretion of

pancreatic digestive enzymes due to loss of intact pancreatic acinar cells, represents one of the most frequent complications of CP[1]. Chronic heart failure describes the complex clinical syndrome where the heart is incapable of maintaining a cardiac output that is adequate to meet metabolic requirements and accommodate venous return[2,3]. There is evidence that CP is associated with an increased risk of cardiovascular diseases (CVD), which may be at least partially explained by sharing many risk factors among these patients[4-7]. Even association between CP and cerebrovascular disease was reported[8]. There is increasing evidence for the involvement of the gastrointestinal (GI) system in congestive heart failure (CHF)[9]. Furthermore, patients with CP and CHF share two other very important clinical conditions: sarcopenia and cachexia[10-13]. Muscle wasting, or sarcopenia, is characterized by loss of muscle mass, loss of muscle strength and impaired functional capacity[10]. The occurrence of malnutrition has been reported as a hallmark of muscle wasting especially in older patients[14,15]. Cardiac cachexia is the clinical entity occurring at the end of the chronic natural course of CHF with complex and multifactorial pathophysiology[16]. Association of PEI in patients with CHF with appetite loss was recently reported[17,18].

MATERIALS AND METHODS

Search strategy and study selection

MEDLINE, Web of Science and Google Scholar databases were searched until May 1, 2019 using the following terms: [(Chronic pancreatitis OR pancreatic exocrine insufficiency) AND (heart failure OR cardiovascular risk OR cardiovascular disease)]. The search was limited to articles in the English language. Eligibility assessment was performed independently by screening the titles and, consequently, the abstracts by 2 reviewers, Nikolic S and Dugic A. All disagreements were resolved by Vujasinovic M and Löhr JM. Review articles, editorials, conference reports, comments on other studies, and animal studies were excluded. Studies on clinical association between CP and heart diseases were included. Of the selected articles, the full texts, as well as the reference lists, were reviewed independently ("snowball-strategy") by three authors (Nikolic S, Dugic A and Vujasinovic M). The selection process of the articles for this review is summarized in Figure 1.

Data collection process and data items

This review was limited to the question of whether there is a connection between CP and CVD in patients older than 18 years at the onset of CVD. The following characteristics were extracted from the publications included: Year of publication, country of origin, study design, number of patients, demographics of patients included and study results.

Interventions made in all of the included studies were diagnostic measures needed for establishing CVD in patients with CP and vice versa. CHF was assessed by echocardiography[3]. Diagnosis of CP was made upon clinical data and pancreatic imaging[1]. Diagnosis of PEI was established by measuring fecal elastase in stool or a C-labeled mixed triglyceride breath test. Control patients were either healthy individuals or were matched with the study group. The exception is the study by de la Iglesia where controls had CP only, whereas the study group had CP and PEI[4].

RESULTS

Study selection

Overall, 1166 citations were retrieved; 1145 were rejected based on title, abstract relevance or duplication; 21 articles were fully reviewed. After further review, an additional 13 full-text articles were excluded due to reasons stated in Figure 1. Final analysis included 8 studies[4-6,17-21]. Characteristics of studies on PEI in patients with CHF are summarized in Table 1. Table 2 shows characteristics of studies on CVD in patients with CP. Figure 2 shows possible association between cardiovascular and pancreatic disease.

Results of the individual studies

Table 1 and Table 2 synthesize the main results of each individual study included in the systematic research.

Outcomes

Three studies assessed the incidence of PEI in patients with CHF as a primary

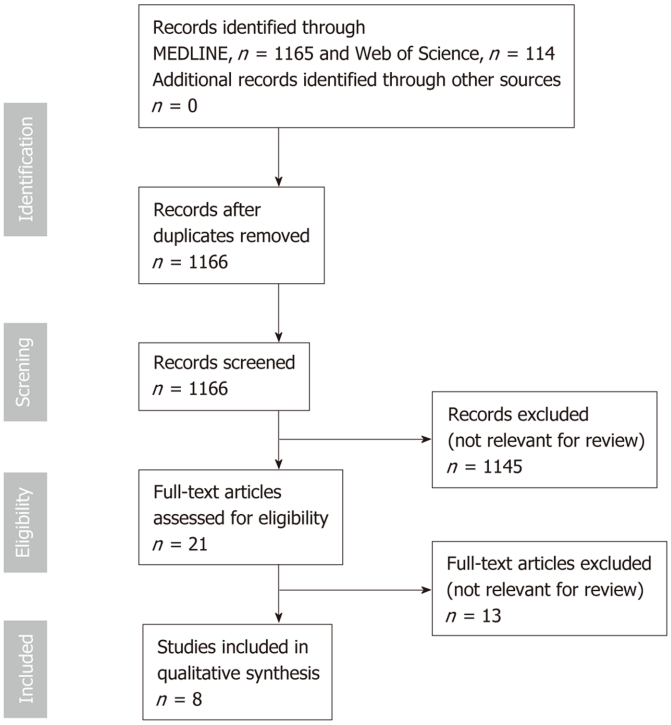


Figure 1 Flow chart on study-selection process.

outcome[17-19] and five studies assessed incidence of cardiovascular complication (acute or chronic coronary lesion, carotid atheroma, peripheral arterial lesion) in patients with CP[4-6,20,21]. Improvement of appetite loss by supplemented pancreatic enzymes was investigated as a secondary outcome in the study by Xia *et al*[17]. The study by de la Iglesia *et al*[4] examined the association of PEI and cardiovascular risk in patients with CP as a primary outcome. The primary outcome measure in most studies was the mean difference between control and patient groups. In studies by Hsu *et al*[6] and Wong *et al*[8], time to vascular event was measured and result represented as a hazard ratio.

DISCUSSION

Congestive heart failure is a progressive disease that causes ischemia and congestion in peripheral tissues and may result in function loss in many organs such as the kidney, liver, stomach and intestine[17]. Nausea and lack of appetite may also occur as blood is shifted from the GI tract to the more vital organs[2]. Susceptibility of the pancreas to ischemic injury in shock, malignant hypertension and after cardiac surgery is well known[22-25]. The splanchnic circulation normally receives approximately 20%-30% of the cardiac output[26,27]. In patients with CHF, the splanchnic circulation is decreased, and if this state is prolonged, tissue damage to the splanchnic organs is possible, especially in pancreas that are highly vascularized organs[22,28].

Pancreatic exocrine insufficiency in patients with heart failure

Appetite loss and malnutrition are well known and highly prevalent in patients with CHF and an important risk factor for morbidity and mortality[29,30]. PEI refers to an insufficient secretion of pancreatic enzymes (acinar function) and/or sodium bicarbonate (ductal function), mostly associated with various pancreatic illnesses but could be associated even with extra pancreatic diseases[1].

Earlier, we performed a prospective study on 87 patients with CHF, using fecal elastase-1 (FE-1) as a diagnostic tool for diagnosis of PEI[18]. The mean time from the confirmation of chronic heart failure to inclusion in the study was 4 years and PEI was diagnosed in 6.9% of patients suggesting a possibility that PEI occurred because of decreased splanchnic circulation in CHF patients. Additionally, the clinical significance of PEI was assessed in this study by using a complete laboratory serum nutritional panel showing decreased levels in one or more nutritional serum markers (vitamin D, selenium, phosphorus, zinc, folic acid, and prealbumin) in all of the

Table 1 Studies on pancreatic exocrine insufficiency in patients with chronic heart failure

Ref.	*n*	Mean age (yr)	Method used	PEI (%)
Xia *et al*[17], 2017, China	All patients: 104 (85.6% males) NYHA I/II: 32 NYHA III: 42 NYHA IV: 30	70.4	FE-1	All patients: *n* = 59 (56.7%) NYHA I-II: Mild/moderate: *n* = 7, severe: *n* = 1; NYHA III: Mild/moderate: *n* = 15, severe: *n* = 14; NYHA IV: Mild/moderate: *n* = 10, severe: *n* = 12
Vujasinovic*et al*[18], 2016, Slovenia	All patients: 87 (64.4% males) NYHA II: 54 NYHA III: 33	74.7	FE-1	All patients: *n* = 6 (6.9%), mild/moderate PEI: *n* = 3, severe PEI: *n* = 3, NYHA II: *n* = 3, NYHA III: *n* = 3
Özcan *et al*[19], 2015, Turkey	All patients: 52 (61,5% males) NYHA I/II: 32 NYHA III/IV: 20	67.5	FE-1	All patients: *n* = 21 (40.4%) NYHA I/II: Mild/moderate PEI: *n* = 3, severe PEI: *n* = 4 NYHA III/IV: Mild/moderate PEI: *n* = 4, severe PEI: *n* = 10

n: Number of patients; FE-1: Fecal elastase-1; PEI: Pancreatic exocrine insufficiency; NYHA: New York Heart Association classification.

patients tested with PEI[18].

Özcan *et al*[19] investigated FE-1 levels (as an indicator of pancreatic exocrine function) and blood ghrelin levels (which affect eating, sleeping, cell proliferation, the cardiovascular system, and carbohydrate energy metabolism in patients with CHF as well as the pancreatic exocrine function) in 52 patients with acute decompensated heart failure and compared them with 31 healthy patients in the control group. The authors reported significant difference in FE-1 levels between the control and NYHA I/II patients *vs* NYHA III/IV group. In patients with advanced heart failure, ten patients (50%) had severe, and four patients (20%) moderate PEI, whereas two- thirds of the controls and patients with mild heart failure had normal pancreatic function. However, there was no statistically significant difference for ghrelin levels[19].

Xia *et al*[17] attempted to detect the association between PEI (measured by FE-1 levels) and CHF-induced appetite, which was tested by the simplified nutritional appetite questionnaire. PEI was diagnosed in 56.7% of 104 patients with CHF and in none within the control group (n = 20) of patients with normal heart function. In the very important second part of this study, patients with CHF and PEI were treated with pancreatic enzyme replacement therapy (PERT) in the form of pancreatin (30000 units per day) and compared with the CHF and PEI patients treated with a placebo. After a 4-wk treatment, pancreatin significantly improved the appetite loss in the treatment group, indicating that PERT can attenuate the appetite loss in CHF and give the strongest evidence so far in the association of PEI with appetite loss in patients with CHF[17].

Cardiovascular risk in patients with CP

The association between CP and CVD has received little attention in the past. In 1975, Tuzhilin *et al*[20] reported a study on cardiovascular lesions in 98 patients with CP and 32 control subjects, analyzing serum amylase, trypsin, trypsin inhibitor, elastase, plasma recalcification time, plasma heparin tolerance, blood fibrinogen level, fibrinolysis activity and capillary permeability to protein and water. They observed a marked correlation between the clinical symptoms in CP and chronic coronary insufficiency, probably because of pancreatic enzymes and their inhibitors that profoundly affected blood coagulability and appear to influence the course of pancreatic inflammation.

In 1982, Gullo *et al*[5] prospectively investigated 54 consecutive CP patients and 54 control subjects for the presence of cardiovascular lesions. Clinical and laboratory evidence of arterial involvement was found in 18 patients (33%) and in 5 controls (9%) ($P < 0.01$), concluding that patients with CP have more frequent cardiovascular lesions that tend to develop at an earlier age, compared to the general population (there were no differences between the two groups for major risk factors like arterial hypertension, smoking habits, or blood lipid abnormalities).

Lee *et al*[21] recently performed an interesting retrospective observational study on 32 patients with alcohol related CP and type 3 c diabetes mellitus (diabetes secondary to pancreatic disease) in whom panoramic (dental) images were taken and compared

Table 2 Studies on cardiovascular diseases in patients with chronic pancreatitis

Ref.	*n*	Mean age (yr)	Results
Tuzhilin *et al*[20], 1975, Union of Soviet Socialist Republics/United States	98	Not reported	Marked correlation between the clinical symptoms in CP and chronic coronary insufficiency Pancreatic enzymes and their inhibitors profoundly affected blood coagulability and appear to influence the course of pancreatic inflammation
Gullo *et al*[5], 1982, Italy	54 49 (90.7%) males	44.2	Arterial lesions were found in 18 patients (33.3%) and in five controls (9.3%) ($P < 0.01$) No differences were found between the two groups for arterial hypertension, smoking habits, or blood lipid abnormalities
Hsu *et al*[6], 2016, Taiwan	17405 14418 (82.8%) males	48.3	The overall incidence of acute coronary syndrome was 2.15-fold higher in the CP cohort than in the non-CP cohort (4.89 *vs* 2.28 per 10,000 person-years) with an adjusted hazard ratio of 1.40 (95% confidence interval 1.20-1.64) Compared with individuals without CP, patients with CP aged ≤ 39 years exhibited the highest risk of acute coronary syndrome CP may become an independent risk factor for acute coronary syndrome
Lee *et al*[21], 2018, United States	32 (100%) males	61.7	Statistically significant association between a diagnosis of alcohol-related CP and diabetes mellitus, and the presence of an atheroma (calcified carotid artery plaques) on the panoramic image, in comparison with the rate manifested by the historical general population cohort (25% *vs* 3%; $P < 0.05$)
de la Iglesia *et al*[4], 2018, Spain	430 340 (79%) males	47.8	Together with known major cardiovascular risk factors like smoking and hypertension, pancreatic exocrine insufficiency is significantly associated with the increased risk of cardiovascular events in patients with CP

CP: Chronic pancreatitis.

to a historical cohort of healthy patients. The prevalence rate of calcified carotid artery plaques (25%) was significantly higher than the rate (3%) in the control group.

Although DM is common in CP and is a well-known risk factor for arteriosclerosis, the link between CP and CVD seems to depend on other mechanisms[31]. Chronic inflammation has been found to be associated with accelerated atherosclerosis and increased risk of CVDs[32]. The pancreatic changes at an advanced age are considered to be related to atherosclerosis (of small vessels)[15]. This concept of "senile pancreatitis" was first described by Ammann *et al*[33] and in most cases has a silent and mild course[34].

In a prospective, longitudinal cohort study, Spanish colleagues evaluated the risk of cardiovascular events and the impact of PEI in a cohort of 430 CP patients with the mean follow-up of 8.6 years[4]. The study demonstrated, for the first time, that PEI is an independent risk factor significantly associated with an increased risk of cardiovascular events.

Hsu *et al*[6] conducted a nationwide retrospective cohort study in Taiwan to determine the risk of acute coronary syndrome (ACS) in patients with CP. In total, 17405 patients with CP and 69620 individuals without CP were followed for 84430 and 417426 person-years showing that overall ACS incidence was 2.15-fold higher in the CP cohort than in the non-CP cohort. Interestingly, the highest risk of ACS was observed in patients aged ≤ 39 years. Here the increased risk was thought to be

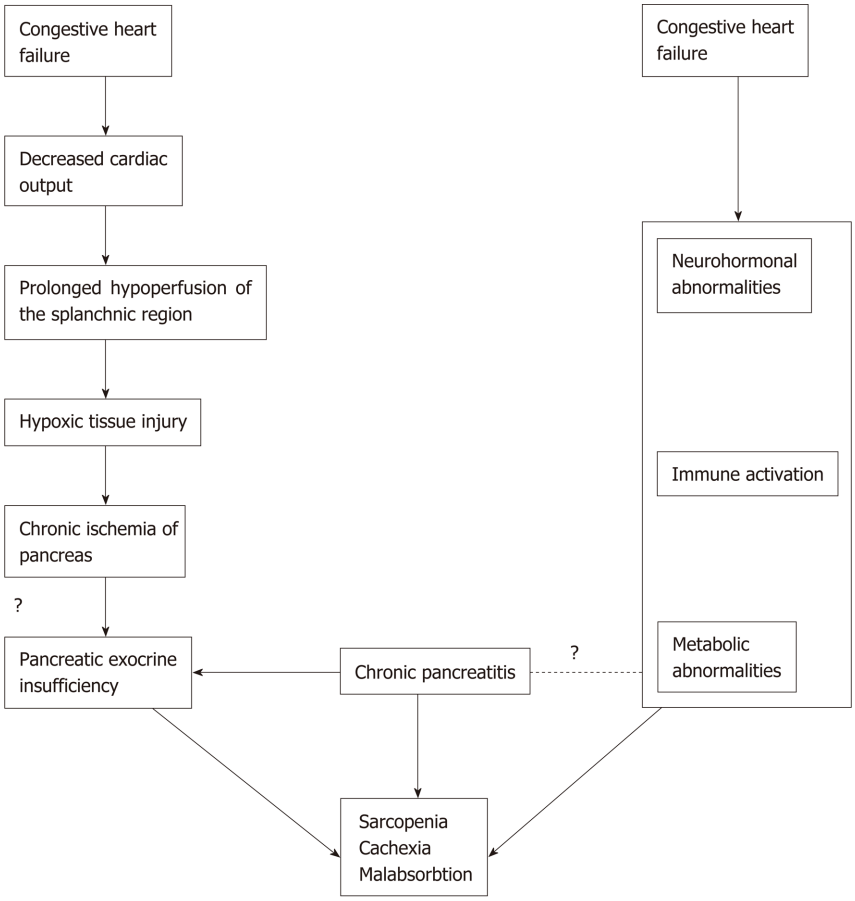


Figure 2 Possible association between cardiovascular and pancreatic disease.

caused by inflammation leading to endothelial dysfunction and progress of unstable plaque. In the similarly conducted retrospective population-based cohort study from Taiwan, Wong *et al*[8] reported association of CP with increased risk of subsequent cerebrovascular disease. The overall incidence of cerebrovascular disease among 16672 patients with CP was 1.24-fold greater than in the non-CP patients.

In conclusion, so far, research on association between heart and pancreas disease has received little attention and its role in pathogenesis is not fully elucidated. However, studies presented in this article indicate an important association that should be further investigated. Patients with CP/pancreatic exocrine insufficiency and chronic heart failure (especially right ventricular dysfunction) share similar clinical symptoms like abdominal pain, anorexia, nausea and bloating[1,2]. Interplay between malnutrition (intake driven) and cachexia (disease driven) can also be seen in both cardiac and pancreatic patients, as well as in sarcopenia (muscle wasting)[1,10,11,16,35]. Current evidence implicates possible association between PEI and malnutrition in patients with CHF. Chronic pancreatic tissue hypoxia and consequent injury is likely to contribute to malnutrition and cachexia in patients with CHF; however, too simplistic of an explanation should be avoided. Future prospective studies on this topic are necessary, especially using diagnostic methods for PEI other than FE-1, like the ^{13}C-trygliceride breath test, secretin enhanced magnetic resonance cholangiopancreatography and serum nutritional markers[1].

On the other side, besides well-known risk factors, CP and PEI seem to be independent risk factors associated with an increased risk of CVD. However, most of the studies so far have been performed on patients with alcohol related CP, and in males. Future studies on CP patients with other etiologies and female patients would be of interest.

ARTICLE HIGHLIGHTS

Research background

Chronic pancreatitis (CP) is a persistent inflammation of the pancreas and with time fibrosis develops. Pancreatic exocrine insufficiency (PEI) due to loss of intact pancreatic acinar cells, represents one of the most frequent complications of CP. Chronic heart failure is a complex clinical syndrome where the heart is incapable of maintaining a cardiac output that is adequate to meet human metabolic requirements. Association between CP and heart disease was reported.

Research motivation

Despite sharing risk factors for atherosclerosis among patients with cardiovascular diseases (CVD) and CP, it has been suggested that CP may be an independent risk factor for development of CVD. At the same time, it seems that congestive heart failure (CHF) and CP share the responsibility for the development of important clinical entities such as sarcopenia, cachexia and malnutrition consequences of cardiac cachexia and PEI, respectively.

Research objectives

The objective of our systematic review was to explore all current evidence regarding the association between CP and heart disease such as CVD and CHF.

Research methods

MEDLINE, Web of Science and Google Scholar were independently searched by two investigators with the aim to identify eligible studies where the connection between CP and CVDs was researched. The primary outcomes were: (1) Incidence of cardiovascular event [acute coronary syndrome (ACS), chronic coronary disease, peripheral arterial lesions] in patients with established CP; and (2) Incidence of PEI in patients with CHF. The primary outcome measure in most studies was the mean difference between control and patient groups.

Research results

Eight studies were eligible for this review. Studies regarding PEI and CHF showed an important incidence of PEI as well as associated malabsorption of nutritional markers (vitamin D, selenium, phosphorus, zinc, folic acid, and prealbumin) in patients with CHF. However, after substitution of pancreatic enzymes, it seems that, at least, loss of appetite was attenuated. On the other side, studies investigating cardiovascular events in patients with CP showed that CP is associated with an increased risk of CVD (a 2.5-fold higher incidence of ACS). Also, CP with concomitant type 3c diabetes had statistically significant higher incidence of carotid atherosclerotic plaques in comparison to patients with diabetes mellitus of other etiologies. When other risk factors for atherosclerosis (hypertension, smoking, and dyslipidemia) were matched, patients with CP had significantly higher incidence of arterial lesions. Moreover, one recent study showed that PEI is significantly associated with the risk of cardiovascular events in patients with CP.

Research conclusions

Chronic pancreatic tissue hypoxic injury driven by prolonged splanchnic hypoperfusion is likely to contribute to malnutrition and cachexia in patients with CHF. On the other hand, CP and PEI seem to be an independent risk factor associated with an increased risk of cardiovascular events.

Research perspectives

Interplay between malnutrition (intake driven) and cachexia (disease driven) can be seen in both cardiac and pancreatic patients, as well as in sarcopenia (muscle wasting) Current evidence implicates possible association between PEI and malnutrition in patients with CHF as well as CP with or without PEI being an independent risk factor for CVD. However, too simplistic explanations should be avoided. Future prospective studies on this topic are necessary, especially using diagnostic methods for PEI other than fecal elastase-1, like the ^{13}C-trygliceride breath test, secretin enhanced magnetic resonance cholangiopancreatography and serum nutritional markers.

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