SYSTEMATIC REVIEW AND META-ANALYSIS

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The Role of Adipokines in Chronic Pancreatitis. A Systematic Review and Meta-Analysis

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ABSTRACT

Background & Aims: Adipokines are among the biomarkers that have been studied in chronic pancreatitis (CP), as well as in pancreatic cancer (PC). So far, the existing findings are contradictory and inconclusive. Therefore, we assessed the levels of three major adipokines in CP in comparison to controls and PC, adiponectin, leptin, and resistin.

Methods: A systematic electronic search was carried out in November 2022 using PubMed, Embase, and Scopus, reviewing observational studies. By using the Newcastle-Ottawa Scale, the included studies' quality was evaluated (NOS). In the examination of the estimated overall effect size, we employed the random-effects model in conjunction with the mean difference (MD) analysis. The MD with 95% confidence interval (CI) served as the primary summary outcome.

Results: Our systematic review included a total of 14 studies, out of which nine were considered in our meta-analysis. A significant MD related to leptin levels in CP patients vs. controls (-1.299, 95%CI: -2.493 - -0.105), resistin levels in CP patients vs. controls (8.356, 95%CI: 3.700-13.012), and adiponectin levels in PC patients vs. controls (11.240, 95%CI: 5.872-16.60) was reported. However, no significant MD was reported in leptin levels between CP vs. PC patients (-0.936, 95%CI: -3.325-1.454), as well as adiponectin levels in CP patients vs. controls (0.422. 95%CI -5.651-6.535]) and in CP vs. PC patients (-6.252, 95%CI -13.269-0.766).

Conclusions: CP was significantly associated with decreased leptin levels and increased resistin levels. Furthermore, increased levels of adiponectin are associated with PC. Yet, no significant MD was seen for leptin and adiponectin levels between CP and PC patients, and likewise for adiponectin levels between CP patients and controls. Results should be interpreted with caution due to the high heterogeneity among the included studies.

Key words: adipokines – adiponectin – leptin – resistin – chronic pancreatitis – pancreatic cancer.

Abbreviations: BMI: body mass index; CI: confidence interval; CP: chronic pancreatitis; MD: mean difference; NOS: Newcastle-Ottawa Scale; PC: pancreatic cancer; SD: standard deviation; T2DM: type 2 diabetes mellitus; LD: years of living with disability.

INTRODUCTION

Chronic pancreatitis (CP) can lead to severe inflammatory syndrome, with complex abdominal pain and negative long-term effects on the exocrine and endocrine pancreatic function. The diagnosis of CP reduces the quality of life tremendously with the median survival being 20 years [1]. Furthermore, the risk for developing pancreatic cancer (PC) is eight times higher for patients with CP [2]. The combined global incidence of CP in the general population is stated to be 10 cases per 100,000 [3]. As for the moment, early CP cannot be diagnosed with a quick and reliable diagnostic test, but a firm diagnosis may take years to be established. With this given difficulty, the issues generally faced by epidemiological studies are more exacerbated [4, 5].

Environmental, behavioral, genetic, and other risk factors precipitate the development and progression towards a chronic fibro-inflammatory syndrome of the pancreas, a link which is described by the new mechanistic definition of CP [6]. The complex of fibrosis, inflammation, and collagen deposition is evoked by the activation of pancreatic stellate cells. Those cells are further responsible for the expression of cytokines and the synthesis of extracellular matrix proteins [1]. Increased

trypsinogen activation and chronic intra-acinar upregulation of the NF- kB pathway are additional factors contributing to pancreatic function loss [7]. As a response to the destruction of parenchymal tissue up to 40% of the CP patients develop pancreatic pseudocysts in time, leading to severe complications [8].

One significant function of the adipose tissue is its' role as an active endocrine organ, secreting different cytokines, adipokines (also known as adipocytokines), and chemokines. By the secretion of molecules, metabolic processes are controlled, while having an impact on inflammation and endocrine function [9]. The white adipose tissue which lines the visceral organs alters the secretion of adipokines in the case of localized inflammation [10]. Other sources of adipokines are the peripancreatic fat and adipocytes in the pancreatic parenchyma itself [11, 12].

One of the best studied adipokines is adiponectin. It has an anti-inflammatory effect exerted by downregulation of pro-inflammatory cytokines [interleukine (IL)-6 and tumor necrosis factor (TNF)-α] and upregulation of anti-inflammatory cytokines [13]. Furthermore, it is known for increasing the systemic insulin sensitivity, and therefore having an antidiabetic role [12]. Compared to other peptide hormones, the level of adiponectin in the blood is remarkably high; however, it is associated with a lower amount in obesity [12, 14]. In contrast, leptin has prominent pro-inflammatory actions. The excretion of leptin is shown to be increased in several cancers (breast, endometrial, pancreatic and colon). Nevertheless, whether it has a positive or negative influence is still under debate [15]. A link between hyperleptinemia and decreased psoas muscle size in CP is a current topic of research [16]. As a physiological role, it acts in the central nervous system as a mediator for the long-term control of appetite, food intake, and body weight [17]. Another adipocyte-derived protein promoting inflammation is resistin [18]. In particular, elevated levels of resistin are linked to insulin resistance [19].

Despite the fact that numerous studies have examined the role of adipokines and their impact on chronic pancreatitis, the evidence at the moment is still inconsistent. Hence, limiting our knowledge of the physiological and pathophysiological roles of adipokines in CP. Additional reasons for conducting this research include the validation of positive/negative associations found, generating a single summary estimate of the effect, or enhancing the accuracy of earlier estimates. In order to assess the relationship of adipokines and CP and to compare the levels of adipokines between controls, CP, and PC patients, we performed the first systematic review and meta-analysis to the best of our knowledge.

METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement was used for writing this systematic review and meta-analysis.

Data Sources and Search Strategy

We conducted an electronic literature search, evaluating available observational studies on PubMed, EMBASE, and Scopus that assessed the presence of adipokines in CP and PC patients as well as controls. Supplementary file describes in full the search approach that was used. Relevant publications were manually screened for in the references of the papers that were included in order to minimize findings bias. We searched for published articles from inception up to the 17th of November 2022, without applying any search filters or constraints based on time, location, or language. Subsequently, we performed a screening review to evaluate whether the titles and abstracts were appropriate. Papers that matched the inclusion and exclusion criteria underwent a full-text review. Two authors (M.K. and A.I.) separately decided whether the reviewed articles were eligible, and they also independently extracted data from studies that were eligible, settling any disagreements by consensus.

Eligibility Criteria

Inclusion criteria of original articles were as follows: (1) full-text articles of observational cohort population-based/hospital-based, cross-sectional, or case-control designs that assessed adipokine levels in CP patients; (2) adipokine levels assessed from serum or plasma; (3) CP diagnosis according to each study criteria; (4) human studies without restrictions to gender, race or ethnicity; and (5) articles published in English, German, or Romanian languages.

Exclusion criteria were as follows: (1) experimental studies; (2) no specified pancreatitis group with adipokine values; (3) editorials, author replies, letters, commentaries, short surveys, case reports, review articles, practice guidelines, conference abstracts, and abstracts published without a full-text article.

Risk of Bias Assessment in Individual Studies

The authors (M.K. and A.I.) independently assessed the internal validity and bias risk of the included studies using the Newcastle-Ottawa Scale (NOS) [20]. The NOS for cross-sectional studies was used, as the included studies evaluated adipokine levels at a specific point of time, regardless of the study design. Discussion was used to resolve disagreements about specific points in the quality assessment of the included studies. The number of stars each study received determined its score. Upon verification of the selection (up to 4 points), comparability (up to 2 points), and outcome section criteria (up to 3 points), the study was given a score that ranged from 0 to 9 stars. Studies were regarded to be of high quality if they obtained 7 stars or more. The eligibility of the studies was unaffected by the evaluation of methodological quality.

Summary Measures and Synthesis of Results

For the data analyses of the meta-analysis, we used the R with Metafor package (OpenMeta [Analyst]). The mean difference (MD) of the adipokines levels served as the overall summary result. For studies that reported medians and interquartile ranges, we calculated the mean and standard deviation (SD) ranges. This was done in accordance with the instructions in the Cochrane Handbook [21]. We also used the Q test and I2 statistics to evaluate the heterogeneities and inconsistencies among the studies. We considered I2 values of 0% to 40% as not important, 30% to 60% as moderate heterogeneity, 50% to 90% as substantial heterogeneity, and 75% to 100% as considerable heterogeneity, as advised by the

Cochrane Handbook for detecting and assessing heterogeneity. In the examination of the estimated overall effect size, we employed the random-effects model in conjunction with the mean difference (MD) analysis.

RESULTS

The initial search resulted in 635 articles, as depicted in Fig. 1 (PubMed n=27, EMBASE n=107, and Scopus n=560). A total of 61 studies were found to be duplicates and removed. The titles and abstracts of 633 publications were checked in the following stage in order to evaluate them for inclusion and exclusion criteria. The findings of the screening were as follows: (1) 50 reviews, (2) 2 conference abstracts, (3) 128 experimental studies, (4) 5 letters/editorials, (5) 1 guideline, (6) 413 other irrelevant studies to this review topic, and (7 33 article abstracts that met the primary criteria. During the initial screening, 599 studies were excluded. We reviewed and evaluated the full-texts of 32 publications for further eligibility assessment, while two reports were not retrieved. Of these articles, 18 were excluded with reasons as follows: (1) 2 articles conducted in languages other than English, German, or Romanian (Russian language n=1, Ukrainian language n=1) [22, 23], (2) 14 reports were conference abstracts [24-37], (3 one article involved only patients with PC [38], (4) one article was an author reply [39]. A total of 14 articles were included in the qualitative synthesis [16, 40-52], of which 9 articles were included in the quantitative synthesis [16, 41, 42, 44, 45, 47-49, 51].

Study Characteristics

Table I provides an overview of the key characteristics of the included studies. A total of 1,008 individuals were included in this meta-analysis, of whom 357 had CP, 154 had PC, and 497 were controls. The precise calculation of the sex distribution was not possible as two studies lacked information [47, 51]. Out of the specified numbers for gender distribution, CP (n=240) 85% were males and 15% were females, PC (n=124) 49.19% were males and 50.81% were females, and for the controls (n=417) 71.7% were males and 28.3% were females [16, 41, 42, 44, 48, 49]. In a total of 42.08% (n=101) of the CP patients, the underlying cause of CP was specified as being linked to alcohol usage [42, 44, 48, 49]. A total of 10 studies were undertaken in Europe (Poland n=7, Germany n=1, Italy n=1, Ukraine n=1) [40, 42-48, 50, 51], two studies in Asia (India n=1, Taiwan n=1) [41, 49], one study in New Zealand (n=1) [16] and one study in the USA (n=1) [52].

Adipokine evaluation

The usage of the following methods was described; seven out of the nine studies performed the analysis with an enzyme-linked immunosorbent assay (ELISA) kit [41, 44-46, 48, 49, 51]; one out of these studies used radioimmunoassay methods in addition to ELISA [47]; another study evaluated the levels only by radioimmunoassay methods [42]; and one used a multiplexed immunoassay system [16]. In terms of testing samples, 6 studies used serum [41, 42, 44, 45, 49, 51], and 3 studies used plasma [16, 47, 48] to measure adipokine levels.

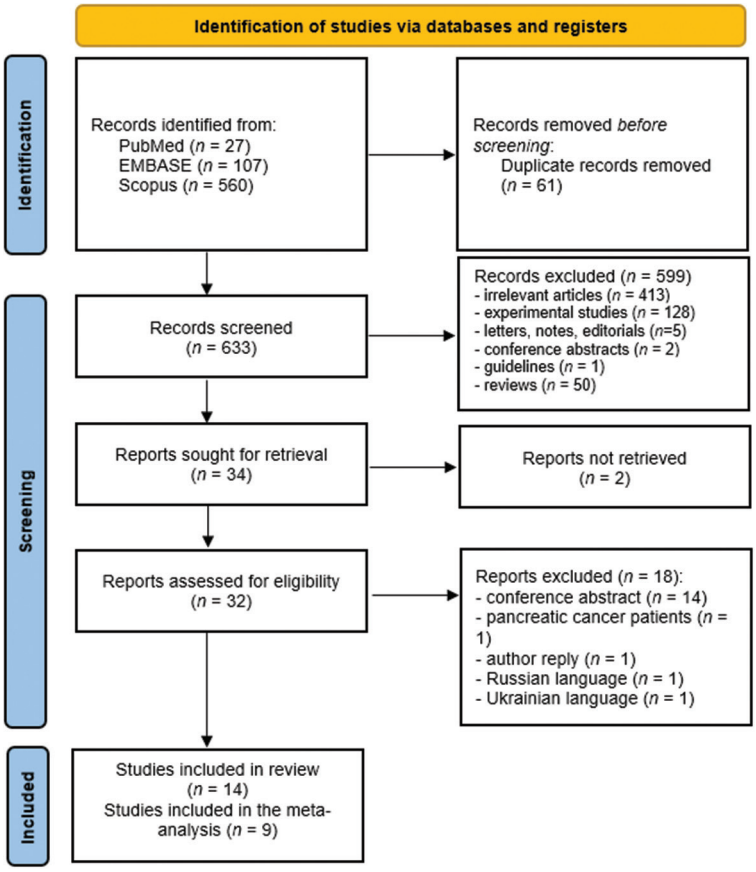

Fig. 1. PRISMA flow diagram with the identification, screening, and included articles.

Table I. Studies assessing adipokine levels in chronic pancreatitis patients

First Author / Year / Country	Study Design	Study Characteristics					Main Findings
		Sample size	Population characteristics	Diagnosis criteria	Adipokine values for cases/ controls	Adjusted factors	
Adrych et al./ Poland/2007	Cross-sectional study	60	Alcohol-related CP and controls	Presence of pancreatic ductal changes on imaging (US, CT, or ERCP), histologically or by Secretin test	Serum leptin level in ng/mL mean ± SD o CP (n = 44) 3.9 ± 2.3 o Controls (n = 16) 6.2 ± 2.8	BMI	Leptin is decreased in CP.
Chang et al./ Taiwan/ 2007	Cross-sectional study	401	CP and PC (unspecific)	Presence of pancreatic calcifications, or confirmed histopathology (surgical or biopsy samples)	Serum adiponectin level in ng/mL mean ± SD o CP (n = 39) 13.74 ± 7.12 o PC (n = 72) 21.14 ± 10.61 o Controls (n = 290) 5.86 ± 4.86	Age, sex, trans-aminases, bilirubin, and BMI	Adiponectin is elevated in PC and CP.
Adrych et al./ Poland/ 2008	Cross-sectional study	70	Alcohol-related and non-alcohol-related CP and controls	Presence of pancreatic ductal changes on imaging (US, CT, or ERCP), histologically or by Secretin test	Serum adiponectin level in µg/mL mean ± SD (range) o CP (alcohol-related) (n = 44) 10.2 ± 4.6 (2.2-22.2) o CP (non-alcohol-related) (n = 10) 9.7 ± 6.2 (5.6-24.4) o Controls (n = 16) 10 ± 3.3 (6.0-17.5)	-	CP is linked to decreased leptin and has no effect on adiponectin.
Adrych et al./ Poland/ 2009	Cross-sectional study	39	Alcohol-related CP and controls	Presence of pancreatic ductal changes on imaging (US, CT, or ERCP), histologically or by Secretin test	- Serum adiponectin level in µg/ml mean ± SD (range) o Controls (n = 16) 10 ± 3.3 (6-18) o CP (n = 23) 9.8 ± 5.1 (2.2-17) - Serum leptin in ng/mL mean ± SD o Controls (n = 16) 6.2 ± 2.7 (1.1-12) o CP (n = 23) 3.6 ± 1.7 (0.9-6.9)	-	Resistin is increased and leptin decreased in CP. Adiponectin does not differ.
Pezzilli et al./ Italy/ 2010	Cross-sectional study	75	CP, pancreatic adenocarcinoma and intraductal papillary mucinous tumor of the pancreas (IPMT)	CP: diagnosed by Marseille –Rome criteria (not further specified); PC: not specified	Serum leptin in ng/mL mean ± SD (original in pg/ml) o CP (n = 23) ▪ Males 7.974 ± 12.822 ▪ Females 13.252 ± 7.351 o Pancreatic adenocarcinoma (n = 34) ▪ Males 3.512 ± 4.087 ▪ Females 11.072 ± 9.491 o Pancreatic IPMT (n = 12) ▪ Males 17.324 ± 10.862 ▪ Females 47.233 ± 57.223	-	Leptin lower in CP and PC. Adiponectin similar in all groups. Decreased leptin levels related to pain in CP and PC. Adiponectin is significantly higher in CP compared to PC
Adrych et al./ Poland/ 2012	Cross-sectional study	80	CP (most of them alcohol-related) and controls	Presence of pancreatic ductal changes on imaging (US, CT, or ERCP), histologically or by Secretin test	- Serum resistin in ng/ml mean ± SEM o CP (n = 40) 5.5 ± 0.91 o Controls (n = 40) 2.4 ± 0.17	-	Resistin and chemerin are elevated in CP
Selig et al./ Germany/ 2012	Cross-sectional study	120	CP and controls (unspecific)	Pancreatic duct changes, parenchymal alterations; in addition to a typical clinical history	Serum adipocyte fatty acid-binding protein (AFABP) in µg/L median (interquartile range) o CP (n = 60) 12.5 (14.6) o Control (n = 60) 20.9 (12.6)	Body weight	Lower levels of AFABP in CP patients (paradoxically)

Table I (continued)

Dranka et al./ Poland/ 2015	Cross-sectional study	90	CP, PC and controls (unspecific)	Not specified	- Plasma adiponectin in mg/ml median (interquartile range) o CP (n = 30) 10.3 (8.4 – 9.1) o PC (n = 30) 24.95 (15.95 – 35.3) o Control (n = 30) 10.4 (8.85 – 22.9) - Plasma leptin in ng/mL median (interquartile range) o CP (n = 30) 2.87 (0.9 - 5.5) o PC (n = 30) 4.18 (2.71 – 6.8) o Controls (n = 30) 4.74 (2.37 – 7.94)	-	Leptin is lower in CP plasma samples compared to PC and CG.Higher concentration levels of adiponectin in the PC group
Gasiorowska et al./ Poland/ 2016	Cross-sectional study	58	CP, PC and controls (unspecific)	CP: a clinical history and anatomical abnormalities on imaging; PC: aspiration biopsy or surgical resection sample	Plasma adiponectin in ng/mL mean (range) o CP (n = 27) 12,227 (8674–16,751) o PC (n = 18) 13,292 (9542–22,446) o Controls (n = 13) 5408 (3933–7799)	Age, gender and BMI	Increased adiponectin is found in CP and PC.
Kamath et al./ India/ 2016	Cross-sectional study	191	CP, recurrent acute pancreatitis (RAP) and controls (unspecific)	Pancreatic calcifications and/or ductal changes, visualized by US, CT, EUS, ERCP or MRCP	Serum resistin in ng/mL median (interquartile range) o CP (n = 81) 23.7 (12.7, 29.5) o RAP (n = 32) 11.6 (7.5, 24.6) o Controls (n = 78) 9.5 (7.8, 12.1)	-	Serum resistin, a promising marker, is elevated in CP.
Kiczmer et al./ Poland/ 2018	Cross-sectional study	for omentin-1 (n = 38), for chemerin (n = 71)	CP (unspecific) Pancreatic ductal adenocarcinoma (PDCA) and controls	Not specified	- Serum omentin- 1 in ng/ml mean ± SD o CP (n = 10) 604.16 (439.86–711.03) o PDAC (n = 20) 582.49 (422.59–663.68) o Control (n = 18) 461.71 (345.42–494.42) - Serum chemerin in ng/ml mean ± SD o CP (n = 10) 260.26 (204.65–312.37) o PDAC (n = 25) 272.01 (221.18–313.98) o Controls (n = 36) 193.32 (173.32–213.87)	-	Increased chemerin in CP and PC. Omentin-1 elevated in PC. No significant MD for both adipokines between CP or PC
Hontsariuk et al./ Ukraine/ 2020	Cross-sectional study	128	CP with and without type 2 DM and controls	Not specified	- Serum leptin in ng/ml mean arithmetic value ± mistake o CP (n = 47) 14.67 ± 1.73 o CP and type 2 DM (n = 40) 45.51 ± 5.12 o Controls (n = 41) 3.7 ± 0.89 - Serum adiponectin in ng/ml mean arithmetic value ± mistake o CP (n = 47) 8.2 ± 0.21 o CP and type 2 DM (n = 40) 4.4 ± 0.3 o Controls (n = 41) 14.21 ± 1.4 - Serum resistin in ng/ml mean arithmetic value ± mistake o CP (n = 47) 9.05 ± 0.1 o CP and type 2 DM (n = 40) 17.2 ± 1.73 o Controls (n = 41) 4.14 ± 0.52	-	Leptin and resistin levels are increased. Highest resistin levels in patients with CP and DM (1.9 times greater), as well leptin higher in CP with DM. Adiponectin is decreased
Park et al./ USA/ 2020	Retrospective analysis	81	CP and controls (unspecific)	CP was defined by definitive changes on cross-sectional imaging, endoscopic ultrasound or histology.	AUC – area under the curve – serum levels o CP vs. Controls (CP (N = 40), Control (N = 41) o GM-CSF, IFN β, leptin, PDGFB, and resistin o AUC (95% CI) 0.86 (0.77-0.94)	-	Leptin is decreased in CP. Resistin is increased in CP

Table I (continued)

Modesto et al./ New Zealand/ 2020	Cross-sectional study	49	CP and controls (unspecific)	Presence of ductal or parenchymal calcifications on imaging and/or Cambridge grade ≥ 3	Plasma leptin in ng/ml median (interquartile range) o CP n=10) 20.0 (0 – 2065.0) o Controls (n=39) 2.9 (0 – 6.4)	age, sex, body composition, physical activity, tobacco smoking, alcohol consumption, comorbidities, and endocrine and exocrine pancreatic functions	Leptin is increased in patients with CP

CP: chronic pancreatitis; SD: standard deviation, BMI: body mass index; PC: pancreatic cancer; SEM: standard error of the mean; AFABP: adipocyte fatty acid-binding protein; RAP: recurrent acute pancratitis, PDAC: pancreatic ductal adenocarcinoma; MD: mean difference; DM: diabetes mellitus; AUC: area under the curve; GM-CSF: granulocyte macrophage colony stimulating factor, IFN β - beta interferon; PDGFB: platelet derived growth factor B.

Leptin – CP vs. Controls

As reported in Fig. 2, four studies evaluated leptin levels in CP patients compared to controls [16, 42, 47, 51]. The overall pooled analysis for studies evaluating leptin levels in CP vs. controls was reported with a MD of -1.299 (95%CI: -2.493 - -0.105) and a moderate heterogeneity of I2=46.25% with a p-value = 0.032.

Leptin – CP vs PC

As shown in Fig. 3, two studies evaluated leptin levels in CP patients compared to PC patients(44, 47). The overall pooled analysis for studies evaluating leptin levels in CP vs. PC patients was reported with a MD of -0.936 (95% CI -3.325, 1.454) and no heterogeneity of I^2 = 18.53% with a p-value = 0.268.

Adiponectin – CP vs Controls

Five studies evaluated adiponectin levels in CP patients compared to controls as reported in Fig. 4 [41, 42, 47, 48, 51]. The overall pooled analysis for studies evaluating adiponectin levels in CP vs. controls was reported with a MD of 0.422 (95%CI: -5.651 - 6.535) and a considerable heterogeneity of I2=97.95% with a p-value < 0.001.

Adiponectin – CP vs PC

Four studies evaluated adiponectin levels in CP patients compared to PC patients as shown in Fig. 5 [41, 44, 47, 48]. The overall pooled analysis for studies evaluating adiponectin levels in CP vs. PC patients was reported with a MD of -6.252 (95%CI: -13.269 - 0.766) and a considerable heterogeneity of I^2=90.8% with a p-value < 0.001.

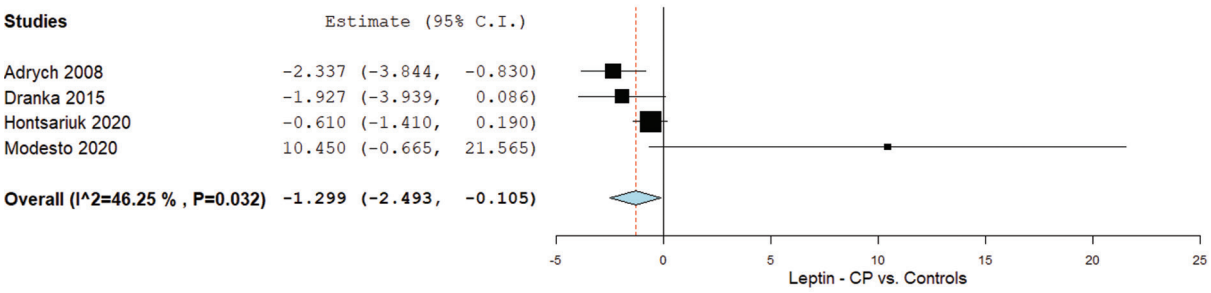

Fig. 2. Leptin levels in chronic pancreatitis patients vs. controls. CP: chronic pancreatitis.

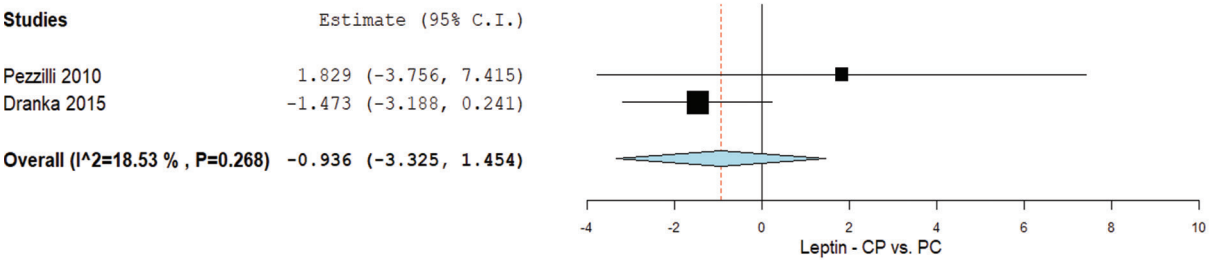

Fig. 3. Leptin levels in chronic pancreatitis vs. pancreatic cancer patients. CP: chronic pancreatitis; PC: pancreatic cancer.

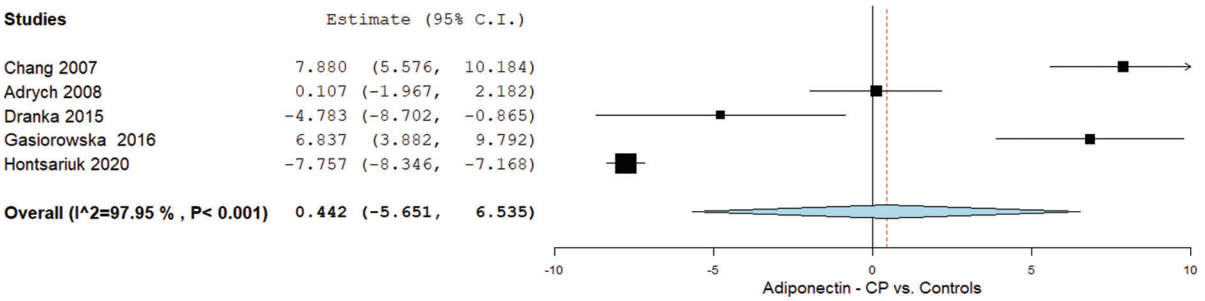

Fig. 4. Adiponectin levels in chronic pancreatitis patients vs. controls. CP: chronic pancreatitis.

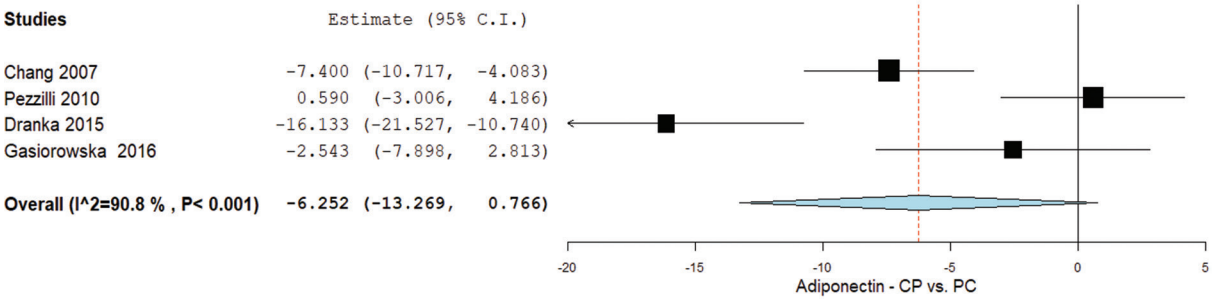

Fig. 5. Adiponectin levels in chronic pancreatitis vs. pancreatic cancer patients. CP: chronic pancreatitis; PC: pancreatic cancer.

Adiponectin – PC vs Controls

Three studies evaluated adiponectin levels in PC patients compared to controls as outlined in Fig. 6 [41, 47, 48]. The overall pooled analysis for studies evaluating adiponectin levels in PC patients vs. controls was reported with a MD of 11.240 (95%CI: 5.872-16.60) and a substantial heterogeneity of I2=83.11% with a p-value < 0.001.

Resistin – CP vs Controls

Two studies evaluated resistin levels in CP patients compared to controls as shown in Fig. 7 [45, 49, 51]. The overall pooled analysis for studies evaluating resistin levels in CP patients vs. controls was reported with a MD of 8.356 (95%CI: 3.700-13.012) and substantial heterogeneity of I2=88.74% with a p-value = 0.006.

Quality Assessment

The included eligible studies were assessed for methodological quality using the NOS for cross-sectional studies, as shown in Supplementary file. The studies that were examined had a clearly stated research topic and an objective. The sample representativeness that was evaluated either by

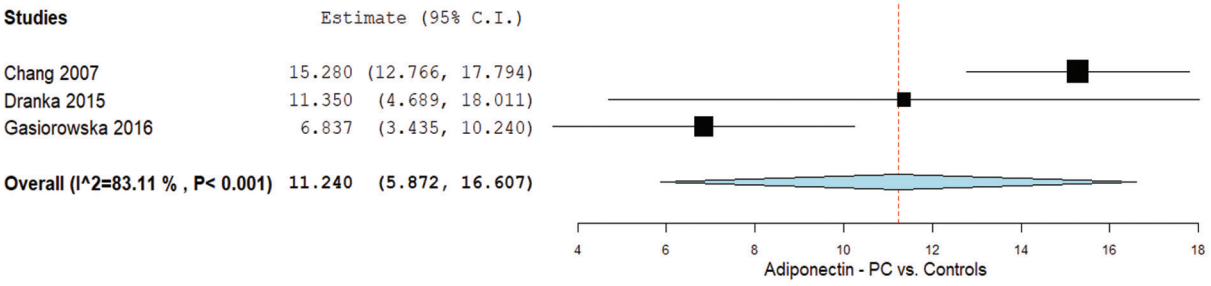

Fig. 6. Adiponectin levels in pancreatic cancer patients vs. controls. PC: pancreatic cancer.

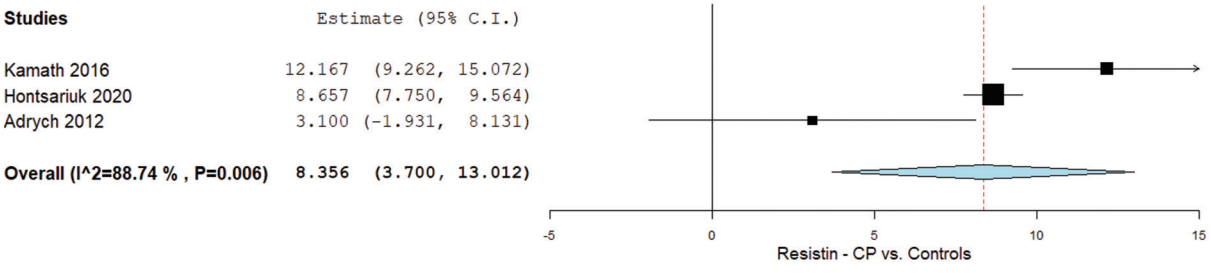

Fig. 7. Resistin levels in chronic pancreatitis patients vs. controls. CP: Chronic pancreatitis.

enrolling participants consecutively or randomly was reported in three articles. All studies stated the measurement of the exposure and outcome in a way that was trusted and legitimate. Moreover, all studies provided an acceptable assessment of the results. Correcting for confounding factors was conducted in three studies. Statistical tests were satisfactory in all included studies. In total, 9 studies received 4 points, 3 studies received 5 points, 1 study received 6 points, and 1 study received 7 points. Overall, only one study was rated as being of good quality.

DISCUSSION

There are a number of specific circulating biomarkers for CP currently under investigation. Adipokines could have the potential to become such a marker, as for the moment CP has no gold standard for diagnosing or differentiating it from other pancreatic diseases. Patients with CP in Central Europe are stated to have an average of 12.5 years of living with disability (YLD) [53]. In these YLD, the quality of life is reduced due to a constant pain syndrome and concurrent comorbidities [54]. In order to detect differences in the levels of several major adipokines (adiponectin, leptin, and resistin) in CP patients, we performed this systematic review and meta-analysis. We found that adipokine levels between CP and controls were decreased for leptin and increased for resistin. However, in the case of adiponectin, there was no significant MD observed. In order to distinguish the levels of adipokines in patients with CP and PC, we analyzed the values of leptin and adiponectin. For both adipokines, no significant MD was found. The comparison of PC patients and controls revealed significantly increased adiponectin levels.

Our results regarding leptin and resistin levels in CP are in accordance with the results of Park et al. [52]. An association between increased resistin levels in CP when comparing them to patients with recurrent acute pancreatitis was shown by Kamath et al. [49]. Hontsariuk et al. [51] performed a subgroup analysis between CP patients with and without type 2 diabetes mellitus (T2DM). Their results showed a 1.9 time increase in resistin levels in patients with T2DM [51]. Resistin has the capacity to increase levels of TNF-α in two specific ways, leading to an exaggeration of the inflammatory response, which might be a pathophysiological explanation for its involvement in CP [17, 55-57]. A correlation between leptin, adiponectin, and body mass index (BMI) has been described. Moreover, a long-standing diagnosis of CP leads to maldigestion with a decrease in BMI [58]. Regarding this, Adrych et al. [42] and Dranka et al. [47] did not see a correlation between adiponectin levels and the patient's BMI in the CP population. We were not able to perform a subgroup analysis for adipokine levels according to the patients' BMI due to insufficient data in the analyzed studies. Gasiorowska et al. [48] and Adrych et al. [42] mentioned that half of their population were smokers. Smoking, which is a frequent etiology for CP, may reduce adiponectin levels as well [59]. Consequently, assessing the impact of smoking on these levels in CP might be of interest for future research. Other adipocyte-derived cytokines associated with CP being under investigation are adipocyte fatty acid-binding protein (AFABP), omentin-1 and chemerin [46, 50].

The comparison of adipokines between CP and PC patients revealed no significant MD. As for leptin, the levels are reported to be decreased in both diseases, CP and PC [60]. So far, the data comparing adiponectin levels in CP vs. PC patients have been inconsistent. This divergence is hard to explain, as BMI levels were similar in both populations; thus, this most likely does not influence our result. In PC patients, increased adiponectin levels are associated with advanced stages of pancreatic cancer, as described by Grote et al. [61]. On one hand, the elevation of adiponectin may be explained by the appearance of cachexia in PC patients, while on the other hand, it might be a compensatory response of insulin resistance in PC [60].

The sex ratio of the included CP population is not consistent with the data up to date. Drake et al. [62] specified this ratio as being two males to one female patient, in contrast to our population, where a proportion of 85% were males. This divergence may be caused by two studies by Adrych et al., which compromised a sole male population [42, 45]. Moreover, this meta-analysis contained a high number of alcohol-related CP; the prevalence for this etiology is about five times higher in males [62]. Neither for sex nor for etiology, a subgroup analysis was not possible as the included studies lacked specific data. One of the remarkable points is that almost all of the included studies used pancreatic imaging to confirm CP. This is in accordance with the ACG guidelines from 2020 [63]. The recommendation is to confirm a clinical picture of a pancreatic inflammatory syndrome with established risk factors by cross-sectional imaging such as computed tomograpgy or magnetic resonance imaging [63].

Regarding the quality assessment of the included studies in our systematic review and meta-analysis, we need to discuss several factors. We described the items which assist the understanding in detail since global quality evaluation tools are not likely to be precise enough to detect bias in articles. More than half of the included studies may be affected by selection bias (either because the population was not precisely defined or because the controls were not chosen from the same group as the cases). In each study, the exposure was reliable and genuine. A point of weakness is that more than half of the studies failed to account for confounding, such as pharmacological treatment or comorbidities. Moreover, the study design used is not able to demonstrate the timing between the exposure and the outcome measure. Therefore, causality between adiponectin, leptin, and resistin with CP or PC cannot be confirmed nor negated.

The heterogeneity observed among included studies in this meta-analysis assessing adipokine levels, including adiponectin, leptin, and resistin, across chronic pancreatitis, pancreatic cancer, and control groups can be attributed to several inherent factors. Firstly, variations in study design, such as differences in participant selection criteria, sample size, and demographic characteristics, contribute to the observed disparities. Additionally, methodological variations in the measurement of adipokine levels, including the use of diverse assay platforms and techniques, may introduce considerable variability. Heterogeneity may also stem from the inherent complexity of the diseases under investigation, as chronic pancreatitis and pancreatic cancer exhibit diverse etiologies and pathological features. Furthermore, the influence of

confounding variables, such as comorbidities, lifestyle factors, and treatment modalities, may further amplify the heterogeneity across studies. Addressing these sources of heterogeneity is crucial for accurate interpretation of the pooled results and underscores the need for standardized methodologies and rigorous study design in future investigations of adipokines in pancreatic diseases.

Regarding the clinical implications of our findings, the significantly decreased leptin levels and increased resistin levels in chronic pancreatitis patients compared to controls may suggest a potential role for leptin and resistin in the pathophysiology of the disease, highlighting the involvement of these adipokines in the inflammatory process associated with the condition. Hence, these adipokines can be incorporated in a complex formula with other biomarkers and scores that can potentially predict the presence of chronic pancreatitis non-invasively. However, their solo use is less likely to be possible at the time being as their values can be altered in several conditions other than CP. As the currently available data did not allow for assessing the role of these adipokines according to disease severity or progression, future research is needed to evaluate their role for prognostic and therapeutic purposes. As most included studies included CP patients diagnosed using imaging techniques, the role of such biomarkers in differentiating between early-stage CP without clearly visible imaging changes remains to be investigated. Additionally, the elevated adiponectin levels observed in pancreatic cancer patients could have implications for early detection or monitoring of the disease.

There are several limitations that need to be further discussed. Most CP patients included in our review were diagnosed using imaging methods, thus presenting changes that are suggestive of late-stage CP. Hence, our findings may not apply to probable or early CP patients that lack radiological changes. Due to the small number of published studies evaluating adipokine levels in CP and PC, we were only able to include a limited number of studies - three to five for each evaluated association. Also, the high heterogeneity of our results might be influenced by the small study number. It is important to mention that small meta-analyses have to deal more often with an I2-bias [64]. Moreover, the variations in assay methods used to measure different adipokines in chronic pancreatitis among the included studies may introduce some degree of heterogeneity into our findings. Consequently, it will be important to evaluate these associations as well in the future using more studies. Given the possibility of methodological errors in the included research, results should be interpreted cautiously.

Our systematic review and meta-analysis also has several strengths. A comprehensive search using three medical databases was conducted, thus, we were able to study associations in a systematic manner. Our review summarizes the present literature objectively and identifies necessary missing data. The included studies were conducted on four continents and represented various ethnic groups, making this analysis a more representative one. The importance of this topic and its clinical significance is outlined due to current insufficient treatment modalities for CP, the associated morbidity and mortality rates, as well as the challenging methods to diagnose this disease. In general, the benefits of adipokines as a biomarker are the easy access from the patient's blood, and in the future, they may play a role in personalized treatments [65]. To our knowledge, this is the first comprehensive review and meta-analysis to assess the relationship between adipokine levels and patients with CP and comparing them to PC patients or controls.

CONCLUSIONS

We report significantly decreased leptin and increased resistin levels in CP patients compared to controls. Moreover, PC patients present significantly increased adiponectin levels. Nevertheless, no significance was found for leptin and adiponectin levels between CP and PC patients, as well as for adiponectin levels in CP patients and controls. Results should be interpreted with caution due to the high heterogeneity between the included studies.

Conflicts of interest: None to declare.

Authors' contributions: A.I. had the idea of the manuscript. M.K. and A.I. independently applied the search strategy and performed the study selection. M.K. and A.I. performed the data extraction. M.K. and M.I. performed risk of bias assessment. A.I. and D.C.L. conducted the statistical analysis. M.K. drafted the manuscript. A.I., M.I., N.A.S., D.C.L., S.L.P., and D.L.D. contributed to the writing of the manuscript. A.I., D.C.L. and D.L.D made substantial contributions to the conception and critically revised the manuscript for important intellectual content. All authors revised the final manuscript and approved the final version.

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