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Adipokines in pancreatic diseases

Adipokiny w chorobach trzustki

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S u m m a r y

Recently, because of the growing number of obese people, the correlation between adipose tissue and numerous disorders has drawn the attention of researchers. The products of adipose tissue, adipokines: leptin, adiponectin, visfatin and resistin, affect lipid metabolism, insulin secretion and inflammatory response. Therefore, it is possible that adipokines take part in the pathogenesis of acute pancreatitis (AP), chronic pancreatitis (CP) and pancreatic cancer (PC). Considering the difficulty of a rapid diagnosis and the lack of efficient and specific biomarker, the potential of adipokines as early predictors of pancreatic diseases course and severity was evaluated. The influence of pancreatic disorders on the body weight and the adipose tissue as well as the ability of inflammatory cells to produce adipokines, make it difficult to establish the cause and effect relationship between the levels of these substances and the inflammatory process and cancerogenesis in pancreas. Multiple studies, including measurements of adipokines plasma concentrations and animal models of pancreatic diseases, attempted to clarify the role of adipokines in the development of AP, PC and CP and their utility as biomarkers.

S t r e s z c z e n i e

Ostatnio, zważywszy na rosnącą liczbę osób otyłych, badacze zwrócili uwagę na związek pomiędzy tkanką tłuszczową a rozmaitymi schorzeniami. Adipokiny, takie jak leptyna, adiponektyna, wisfatyna i rezystyna, będące produktami tkanki tłuszczowej, wpływają na metabolizm lipidów, wydzielanie insuliny i odpowiedź immunologiczną. Jest więc prawdopodobne, że adipokiny biorą udział w patogenezie ostrego (OZT) i przewlekłego zapalenia trzustki (PZT), jak również raka trzustki. Biorąc pod uwagę trudności diagnostyczne oraz brak szybkiego i specyficznego biomarkera, sprawdzono potencjał adipokin jako wczesnych wskaźników przebiegu i stopnia ciężkości chorób trzustki. Wpływ patologii w obrębie trzustki na masę ciała i ilość tkanki tłuszczowej oraz możliwość wydzielania adipokin przez komórki zapalne sprawiają, że trudno jest ustalić związki przyczynowo-skutkowe między stężeniem tych substancji a rozwojem zapalenia i procesu nowotworowego w trzustce. Liczne prace badawcze, między innymi pomiary osoczowych stężeń adipokin oraz badania na zwierzęcych modelach chorób trzustki, starały się wyjaśnić rolę adipokin w rozwoju OZT, PZT i raka trzustki, a także ich przydatność jako biomarkerów.

INTRODUCTION

Pancreatic diseases: acute pancreatitis (AP), chronic pancreatitis (CP) and pancreatic cancer (PC) are severe and life-threatening conditions.

Lately, given the increasing prevalence of obesity, the role of the white adipose tissue and its correlations with multiple diseases was analysed. The adipocyte-derived hormones and cytokines, adipokines, take part in many immunological and metabolic mechanisms that can be related to the pancreatic diseases. In this article we try to evaluate diagnostic and prognostic value of adipokines in AP, CP and PC according to the current research and studies presented in the literature.

THE ROLE OF THE WHITE ADIPOSE TISSUE

The number of obese people and obesity-related health problems increases worldwide. The obesity not only leads to diabetes mellitus, dyslipidemia, arterial hypertension and atherosclerosis (1), but it is also a risk factor for malignancies (2): endometrial (3), renal (4),

colorectal (5), esophageal, hepatocellular, prostate (6) and breast cancer (7). The correlation between obesity and cancer is multifactorial (8). Firstly, the chronic low-grade inflammatory state induced by obesity provokes the immune dysfunction and modifies the levels of proinflammatory and anti-inflammatory cytokines. Secondly, the metabolic disorders: lipotoxicity and insulin resistance, may promote the cancerogenesis (9). Thirdly, the hormonal mechanisms: the changes in steroid and sex-hormones production may lead to hormone-related cancers. In addition to this, the fatty infiltration establishes a proinflammatory milieu and causes organ dysfunction (10). Adipokines produced by the adipose tissue have many endocrine, paracrine and autocrine effects.

The adipose tissue products alter the functions of pancreas (11, 12) which may contribute to the AP, PC or CP. The researchers suggest that the associations between adipokines and pancreatic diseases exist also at the genetic and epigenetic level. The experimental studies with RINm5F insulinoma cells have shown that the activation of the leptin receptor LEPRb provokes the upregulation of inflammation-related genes (13). The adipokines which may have an important role in the pathogenesis of pancreatic diseases are: adiponectin, leptin, resistin and visfatin. Known as a protein encoded by the obese gene, leptin participates in the regulation of energy expenditure as well as food intake and reduces the insulin secretion (14). It also modulates the inflammatory response which is connected with the reduction of TNF-α and the increase of IL-4 production (15). The studies of insulinoma cells revealed transcriptional effects of leptin in pancreatic β cells and an addictive effect of leptin and IL-1β and its proapoptotic role by activation of caspase 3 (13). Adiponectin, takes part in the regulation of glucose and lipid metabolism. It ameliorates the insulin resistance and facilitates glucose control. In addition to the antidiabetic properties, adiponectin has an anti-inflammatory role. It decreases the synthesis of tumor necrosis factor alpha and interferon γ (16) and increases the production of IL-10 and IL-1 receptor antagonist (17). Resistin is another adipokine that influences metabolism and inflammatory response. The proinflammatory potential of resistin was demonstrated by its capacity to induce arthritis in healthy mouse joints (18). Both resitin and visfatin (19) can activate the synthesis of pro-inflammatory agents such as IL-6, IL-1ß and the tumor necrosis factor.

SEARCH FOR THE VALUABLE BIOMARKER

The diagnosis of pancreatic diseases is now based on clinical presentation, serum markers such as amylase, lipase and C-reactive protein, and radiological findings (20). Pancreatic cancer is very lethal, with a low 5-years survival rate: 6% (21). Additionally, symptoms of PC are non-specific and vague, there is no sensitive screening and the treatment is mostly palliative. Therefore, there is a great need to improve prognosis in high risk populations. Because of its high mortality (22) and complications, fast diagnosis of acute pancreatitis is essential. The scales and scores, like: Atlanta criteria, Balthazar CT score or APACHE II score (23), help to choose the right treatment and evaluate the survival prognostic. However, there is no efficient predictor of the severity or the risk of death for AP. A good marker should allow an early prediction of disease course. The differential diagnosis between CP and PC is particularly problematic because of the the lack of specific and remarkable symptoms in both diseases. In addition to this, chronic pancreatitis is a significant risk factor for pancreatic cancer. Adipokines could be a diagnostic tool providing a rapid diagnosis of pancreatic diseases. Moreover, modifiable by behavioural or drug interventions, they may be considered as a therapeutic tool which could be applied in preventive strategy for pancreatic disorders.

THE ACUTE PANCREATITIS AND ADIPOKINES

Acute pancreatitis is characterized by high mortality, wide range of clinical manifestations, local and systemic complications, like: pancreatic necrosis, abscess, fistulas, organ injury, sepsis, cardiovascular failure (24). Serum amylase and lipase concentrations poorly correlate with the course and severity of the disease. Commonly used CRP, despite its good predictive value for the severity of acute pancreatitis, is not a specific marker for AP. Therefore, the prognosis is often based on clinical scores. Various clinical studies have analyzed the connection between obesity and AP. According to the researchers, the higher risk of AP in obese people may result from the accumulation of visceral fat within and around pancreas and a higher expression of cytokines. The adipokine's levels in AP patients were measured to evaluate their diagnostic and prognostic potential. Schäffler et al. (25) measured the serum concentrations of resistin and leptin in patients with mild, moderate and severe AP. Resistin and leptin levels were higher in patients with higher scores in radiological scoring systems (pancreatic necrosis score, Balthazar score). Additionally, the researchers found a positive correlation between leptin levels and CRP concentrations. This allows to consider leptin and resistin as potential markers of disease activity in AP. Daniel et al. evaluated the levels of resistin and visfatin in AP patients (26). The serum concentrations of adipokines were significantly higher than in control group and they correlated positively with CRP levels. On the other hand, these findings are contested by the results obtained by Duarte-Rojo et al. (27) As reported in their analysis of 52 patients with AP, leptin has no value as a prognostic marker of the disease. Leptin serum levels didn't correlate significantly with the severity of AP nor with any other cytokine level (TNF-α, IL-6 and IL-10, IL-8). The lack of relationship between leptin concentrations and the severity of the disease may be due o the predominance of women in the sample. The importance of android fat distribution and lower body mass index in the female patients with severe pancre-

atitis should be considered while interpreting the result of this study. Similarly, in the survey carried out by Tukiainen et al. (28), the comparison of 12 patients with severe and 12 patients with mild AP, demonstrated that the on-admission levels of adiponectin and leptin didn't correlate with the severity of disease. The small number of patients is the main limitation of this study. All these results show that a further research is needed to estimate the role of adipokines as a predictor of the course of AP.

The utility of adipokines in the diagnosis and prognosis of AP was analyzed also in experimental studies. A study on rats with alcohol-induced pancreatitis (29), showed the relationship between plasma leptin concentrations and pancreatic inflammation. The rats with pancreatitis were divided in two groups: acute pancreatitis and chronic pancreatitis according to the histopathological findings. The researchers noticed elevated leptin levels in the AP group, compared to controls. Furthermore, the adipokine's levels remained higher while the inflammation process in pancreas continued (in CP group). These observations suggest that the inflamed tissue could be a local source of this adipokine. As there was no significant difference between leptin concentrations in acute and chronic pancreatitis, the differential diagnosis, based only on the adipokine level was impossible. The study of pancreatitis model in obese mice shows that not only the volume of adipose tissue but also the adipokine levels are important in the course of AP (30). The obese mice developed more severe AP than the lean animals. Additionally, the mice with a defective leptin receptor and elevated leptin concentrations (Lep^{Db}) presented more severe pancreatitis than the mice with a spontaneous ob gene mutation, that produced no leptin (Lep^{Ob}). The findings draw attention to the proinflammatory role of leptin and demonstrate that the adipokine milieu decreases the severity of AP. Potentially, the regulation of adipokine's levels, especially leptin (proinflammatory) and adiponectin (considered as an anti-inflammatory mediator), could change the severity of AP (31). The studies of rats with caerulein-induced pancreatitis (CIP) show higher leptin concentrations in the animals with AP (32). The researchers observed an increase of the leptin mRNA in rats after the induction of pancreatitis. The effect of exogenous leptin was also evaluated: the pretreatment with leptin resulted in plasma amylase, TNF-α and pancreatic weight decrease. The main conclusions that can be drawn from these results are: firstly, the inflamed pancreas could be a local source of leptin, secondly, leptin administration may protect the pancreas against CIP.

THE CHRONIC PANCREATITIS AND ADIPOKINES

The chronic pancreatitis is an inflammatory disease of pancreas, leading to many complications: endocrine and exocrine pancreatic insufficiency, malnutrition, chronic pain, pseudocysts or stenosis of the pancreatic duct (33). It is also an important risk factor for the pancreatic cancer (34). The aetiology and pathogenesis of CP are not yet completely understood. The most well-known etiologic factors is alcohol consumption. Some genetic risk factors were also identified: mutation in the *PRSS1* gene. The immune and inflammatory process are associated with the development of CP.

The levels of leptin, resistin and adiponectin in patients with chronic pancreatitis have been evaluated. The study including 23 male patients with CP showed higher resistin levels, lower leptin levels and similar adiponectin levels comparing to the heathy controls (35). Moreover, the resistin concentrations didn't correlate with Body Mass Index or insulin concentrations in CP patients. The authors of the study suggest that increased resistin level is associated with higher concentrations of tumor necrosis factor α. According to this hypothesis, resistin stimulates TNF-α synthesis in macrophages and mononuclear cells. Consequently, pancreatic stellate cells, activated by TNF-α, produce collagen which leads to pancreatic fibrosis. Another study (36) confirmed decreased concentrations of leptin in CP patients. Leptin is produced by adipose tissue and takes part in the regulation of food intake. Therefore, the researchers suppose that lower serum leptin levels in patients with chronic pancreatitis could be a result of maldigestion, fat loss and the decrease in insulin serum concentrations. An additional research is necessary to confirm this theory and exclude other factors that could affect the serum levels of leptin.

Although leptin is thought to take part in the etiopathogenesis of idiopathic chronic pancreatitis (ICP) by altering pancreatic exocrine function and beta-cell secretion, no difference between leptin concentrations in patients with ICP and healthy control was shown (37). The study demonstrated that leptin level is not correlated with the exocrine and endocrine pancreatic functions, represented by the C-peptide concentration and fecal chymotrypsine.

An early detection of chronic pancreatitis is crucial for the effective treatment. A perfect marker for CP should not only allow a rapid diagnosis and prognosis but also differentiate between chronic pancreatitis and pancreatic cancer. Serum concentrations of adiponectin were significantly more elevated in patients with PC when compared to the control group as well as to the group with CP (38). These findings show the potential of adipokines in the diagnosis of chronic pancreatitis.

THE PANCREATIC CANCER AND ADIPOKINES

As pancreatic cancer is characterised by a high mortality, still an elusive pathogenesis and no efficient treatment, the search for risk factors and markers is crucial (39). Carbohydrate antigen CA 19-9, commonly used as a PC biomarker, is more useful as a survival predictor after pancreatectomy than a screening tool (40). The correlation between PC and obesity was demonstrated (41). The study showed that increased BMI is associated with a low overall survival. In addition to this, another research proved that overweigh and

obesity are correlated with a younger age of PC onset (42). Higher BMI and obesity related complications, such as diabetes mellitus and fatty infiltration of pancreas (43), can be considered as risk factors for PC. In the search for biologic mechanisms of these findings, Lin et al. analyzed the genetic variations of obesity-associated gene (FTO) and the related risk of pancreatic cancer (44). They discovered an increased risk of PC in the group with heterozygous TA and homozygous AA variant of FTO gene. Interestingly, they found no significant correlation between these genotypes and BMI. The role of adipokines in the pathogenesis of pancreatic cancer, was also examined. Gąsiorowska et al. evaluated the levels of leptin, visfatin and resistin in PC patients (45). The main results of this study are: decreased leptin, increased resistin and similar visfatin serum concentrations as compared to the healthy controls. The existence of diabetes, tumor size and distant metastases did not affect the adipokines level. The suggested explanation of the higher resistin concentration is the activation of pancreatic cancer stroma. The inflammatory cells in the activated stroma would then become an accessory source of resistin. As regards lower levels of leptin, participating in glucose homeostasis, they could be related to the βcells dysfunction and deregulated insulin biosynthesis. A study by Jiang et al. presents the correlation between the resistin expression in pancreatic ductal adenocarcinoma samples from 45 patients and the prognosis of the disease (46). Resistin was expressed in 100% of poorly differentiated tumors, less in moderately and well-differentiated ones. The expression of this adipokine was also higher in stages III and IV (66.7%) than in I and II (22.2%). Furthermore, resistin was associated with a shorter relapse-free survival. These results show the potential of resistin as a prognostic factor for PC. The authors notice that resistin level is increased in obesity, insulin resistance and inflammation, considered as important factors of pancreatic cancer progression. Similarly, the role of adiponectin and leptin as markers for PC was evaluated (47). The first observation of this study is the expression of adiponectin receptors in a great majority of PC. Secondly, the researchers reported higher adiponectin and decreased leptin levels in patients with pancreatic cancer. These findings can be interpreted in two ways. First explanation of the changed adipokines concentration would be a response to the disease induced weight loss, cancer cachexia, and compensation of insulin resistance. The second possible conclusion would be that adiponectin and leptin are implicated in the development of PC. To summarise, it is not yet proved what is the cause-effect relationship in the association between adipokines and pancreatic cancer. The reason of higher adiponectin levels in PC patients in the presented analysis seems even more complex if compared to the results of American cohort study (48). Data including five US cohorts demonstrated that low prediagnostic plasma adiponectin was correlated with a higher risk of pancreatic cancer. Another cohort study of male smokers showed that increased adiponectin concentrations before diagnosis were inversely associated with PC (49). Since higher levels of this adipokine are correlated with the lower risk of pancreatic cancer, adiponectin might be possibly considered as a an element of therapeutic strategy for this disease.

CONCLUSIONS

In conclusion, the function of adipokines in pancreatic diseases is not yet understood. The findings of studies are often contradictory and do not allow to explain the role of leptin, visfatin, adiponectin and resistin in the pathogenesis of PC, CP and AP. Moreover, the issues such as cut-off values and the associations with obesity and weight loss, should be considered. Adipokines seem still to have a potential as a marker for pancreatic diseases. Further research is needed to evaluate their value in diagnosis and prognosis of acute and chronic pancreatitis as well as pancreatic cancer.

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