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Short communication

Biochemical markers for diagnosing and monitoring of acute pancreatitis

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Introduction

Pancreatitis is an inflammatory disease of the pancreas which depending on the recurrence, can be classified as: acute, recurrent acute, chronic or recurrent chronic pancreatitis. The mortality rate of acute pancreatitis has remained at about 10% over the years, because of inadequate or late diagnosis. Industrialized countries have estimated an annual incidence rate of 5-12/100.000 for development of chronic pancreatitis (Yadav and Lowenfels, 2013). Acute pancreatitis (AP) occurs due to alcohol abuse, cholelithiasis, pancreatic tumors, drugs, etc. When the pancreatic cells are affected with the pathological process, enzymes and inflammatory mediators are released from them causing damage to the tissues. The clinical presentation involves atypical symptoms and therefore the diagnosis significantly relies on the laboratory analysis. This study summarizes the currently used and recently proposed potential biochemical markers for diagnosis and monitoring of the acute pancreatitis including enzymes, acute phase proteins and mediators of inflammation.

Current and potential markers in laboratory evaluation of acute pancreatitis

The enzymes amylase and lipase, the proenzyme trypsinogen and the C-reactive protein are currently the most used indicators in diagnosing and monitoring of acute pancreatitis. Their serum levels increase correlating with the severity of the disease.

Procalcitonin is a precursor of calcitonin. It is also an important protein of the acute phase with concentrations directly proportional to the severity of the disease, which enable its use as a marker for monitoring and prognosis. Serum amyloid Ais synthesized by the liver upon the action of neutrophils, monocytes, and T cells. It is a protein that is released during inflammation and in the specific case of acute pancreatitis, its levels are expected to increase (Harper and Cheslyn-Curtis, 2011; Silva-Vaz et al., 2020). Interleukins–IL-6 acts as an inducer of hepatic CRP synthesis. In the state of acute pancreatitis, its levels are increased. Studies have confirmed that it is a specific and selective marker of the severity of the disease. The limitation of its use is that the assay is complex to perform. IL-8 is a secondary mediator in neutrophil activation. IL-10 is an anti-inflammatory cytokine used in clinical practice as a marker for milder forms of AP. The serum levels of IL-17 correlate with the severity of AP and is a valuable prognostic factor in assessing disease progression in AP patients (Harper and Cheslyn-Curtis, 2011; Li et al., 2021; Matull etl al., 2006). Tumor necrotizing factor α is a protein released by monocytes, macrophages and acinar cells and is an important mediator of the inflammatory process. TNFα levels rise in the early stages of acute pancreatitis. Matrix metallopeptidase-9 is a class of enzymes belonging to the family of zinc metalloproteinases involved in the breakdown of the extracellular matrix. In acute pancreatitis, the level of these enzymes is increased. Phospholipase A2 is an enzyme released by the pancreas in an inflammatory state. It participates in the formation of lipid mediators of inflammation such as leukotrienes and prostaglandins. In clinical practice, it can be used to predict the degree of tissue necrosis (Harper and Cheslyn-Curtis, 2011). Polymorphonuclear elastase is an enzyme involved in the degradation of the extracellular matrix during the early stages of acute pancreatitis. High levels of this enzyme 24 hours after the onset of symptoms are typical for severe acute pancreatitis (Harper and Cheslyn-Curtis, 2011; Silva-Vaz et al., 2020). Adhesion molecules such as intercellular adhesion molecules 1 (ICAM-1) and

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vascular adhesion protein1 (VAP-1), are mediators of inflammation. Their increased serum levels are employed for early diagnosis of AP (Li et al., 2021). Hydrogen sulfide and substance P have an important role in the development of AP, inducing local vasodilatation and increasing microvascular permeability which lead to the accumulation of leukocytes (Kumar and Bhatia, 2021; Thangaraj, 2016). Carboxypeptidase B activating peptide (CAPAP) is a peptide that is released upon activation of carboxypeptidases. After examination in several studies, it was found that CAPAP levels increased from the onset of symptoms over 72 hours (Harper and Cheslyn-Curtis, 2011; Matull, 2006). Poly-C avid ribonuclease is an enzyme used as a marker for the destruction of pancreatic tissue that has a high specificity in the first 3 days of the disease. It shows correlation with IL-6, IL-8 and TNFα concentrations (Harper and Cheslyn-Curtis, 2011). Hepcidin is a circulating peptide hormone that regulates the entry of iron into plasma. The hepcidin levels increase during inflammation as a result of an increase of IL-6. It was found that hepcidin is a better predictive marker for severe acute pancreatitis compared to CRP (Silva-Vaz et al., 2020). Copeptin is a glycopeptide that is co-synthesized with vasopressin. In patients with acute pancreatitis, its concentration is elevated. Soluble E-selectin is an endothelial activation marker, whereas soluble thrombomodulin (sTM) is an endothelial injury marker. During acute pancreatitis, activated neutrophils release elastase, which damages the endothelium and release of sTM and sES occurs. They can be used as predictive markers of mortality. Endothelin I is a peptide produced by vascular endothelial cells. Elevated levels of endothelin I have been found to be associated with AP, and it can be used as a marker for the severity and monitoring of the treatment (Silva-Vaz et al., 2020). Adipokines are cytokines produced in white adipose tissue as well as in peripancreatic fat and involved in inflammatory response. Peripancreatic fat necrosis in acute pancreatitis is associated with the development of severe acute pancreatitis, multiple organ failure and mortality. It is hypothesized that peripancreatic necrosis can cause the massive release of adipokines into the bloodstream, which is the basis for their use as predictors of clinical course and complications of acute pancreatitis (Karpavicius et al., 2016). Melatonin has been suggested by a number of studies to play a protective role in AP by activating antioxidant activity. It also reduces gene expression and synthesis of proinflammatory cytokines. The variations of melatonin concentration in the serum might reflect the degree of AP severity to some extent, which leads to its use as a marker (Jin et al., 2013).

Conclusion

Recent scientific advancements have proposed novel biomarkers as more specific than those already in use, including interleukins 6, 8 and 10, procalcitonin, serum amyloid-A, tumor necrotizing factor α, matrix metallopeptidase-9, phospholipase-A2, polymorphonuclear elastase, trypsinogen 2, etc. In addition to that, substances such as carboxypeptidase B activating peptide, poly-C avid ribonuclease, tissue factor, hepcidin, copeptin, angiopoietin-2, adhesion molecules, hydrogen sulfide and others, can potentially be used as biomarkers with further research. Further studies investigating these markers among large cohorts with specifically designed protocols are expected to elucidate their precise association with the AP pathology and define their applicability as diagnostic, prognostic markers or targets for effective drug therapy.

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