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Lymphocyte ratio, oxidative stress, cell death and metabolic profiling in acute pancreatitis: implications for disease monitoring

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ABSTRACT

Acute pancreatitis (AP) is the autodigestion and inflammation of the pancreas that clinically presents with nausea, vomiting, abdominal pain, and increased amylase and/or lipase levels. Mild acute pancreatitis (MAP) is associated with no organ dysfunction and quick recovery. Moderately severe acute pancreatitis (MSAP) has transient organ dysfunction, while severe acute pancreatitis (SAP) is characterized by a significant systematic inflammatory response associated with varying degrees of organ dysfunction. Current systems use many variables to diagnose AP, which are unsuitable for identifying high-risk patients, prognosis, and management. This study aimed to identify metabolic indicators for monitoring AP severity by measuring the CD4:CD8 ratio, apoptosis, hydroperoxides, and metabolites, key pathological responses to the activated immune system. Fifty patients of different severities of AP as well as ten healthy controls (HCs) were recruited from the Chris Hani Baragwanath Academic Hospital. Whole blood samples were collected from the patients within 72 hours (Day 1) of experiencing epigastric pain and every 48 hours for an additional 3 days (Days 3, 5 and 7). The peripheral blood mononuclear cells (PBMCs), plasma and serum were prepared according to standard operating procedures. Flow cytometry was used to quantify the CD4:CD8 ratios while apoptotic gene expression, hydroperoxides and metabolites were analyzed by polymerase chain reaction (PCR), DEPPD assay and nuclear magnetic resonance (NMR) spectroscopy, respectively. As expected, the HCs and the MAP groups had the highest percentage of CD4:CD8 compared to the other AP severity groups. *Caspase 7* expression was high in MAP compared to the HCs, although not statistically significant, while its expression in MSAP patients was statistically significant ($p = 0.0029$) compared to the HCs. Over time, the expression of *caspase 7* expression in MSAP patients increased on day 5 ($p = 0.00994$) and slightly on day 7 ($p = 0.0249$). The expression of *caspase 7* in SAP patients decreased over time from day 5 to day 7. The MSAP group displayed the highest levels of hydroperoxide on day 5 with statistical significance to the HC than the other groups in both serum ($p = 0.0012$) and plasma ($p = 0.0008$), between the SAP and the HC in serum on day 5 ($p = 0.0009$) as well as in plasma ($p = <0.0001$ between MAP and the HC. An unsupervised analysis of metabolites separated the AP patients into two clusters consisting of MAP+MSAP and another of MSAP+SAP patients. The main metabolites differentiating the groups were phenylalanine 0.54 ($p< 0.001$); mannose 0.57 ($p< 0.001$); lactate 0.67 $p< 0.001$), acetoacetate 0.63 ($p<0.001$), 3-hydroxybutyrate 0.46; ($p< 0.003$) lipid alpha-CH2 0.45($p=0.006$) with AP severity. Ascorbate 0.46 ($p< 0.003$); glutamine -0.55 ($p<0.001$); methanol -0.46 ($p< 0.003$); ethanol -0.64 ($p< 0.001$); lipid=CH-CH2-CH=-0.55($p<0.001$), lipid beta-CH2 -0.52 ($p<0.001$), lipid-CH3 -0.44($p=0.005$) and protein-NH -0.75 ($p<0.001$) decreased as severity increased. Taken together, the measured parameters i.e., CD4:CD8 ratio, apoptosis, ROS, and metabolites, suggest that as AP severity increases, integrating immune and metabolomics data may help in understanding the pathophysiological conditions of AP for early stratification, management, and prognosis of patients. MSAP represents the earliest shift toward progression without the comorbidities associated with SAP.