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The utilization of kallistatin as a novel biomarker for the determining of serum in diagnosing liver diseases of animals

Abstract

Kallistatin is a novel biomarker, a plasma protein produced by the liver, utilized for diagnosing liver diseases in both humans and animals. The indicator can serve as a diagnostic indicator for assessing the extent of liver cell damage and as a marker for chronic liver diseases. The level of kallistatin decreases significantly in cirrhosis and is directly related to the biochemical indices of blood. Furthermore, the lower the level of kallistatin, the more pronounced the degree of liver cell damage. However, this indicator has not been sufficiently investigated in laboratory diagnosis, particularly its relationship to liver disease. Further research is needed to elucidate its diagnostic potential and clinical significance in liver pathology. In addition, for animals with chronic liver disease, it has been found that kallistatin can serve as a useful and reliable diagnostic indicator of liver health, particularly in cases of cirrhosis.

Keywords: kallistatin, diagnosing liver diseases, liver fibrosis, biomarker, cirrhosis

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Introduction

To date, there is a paucity of research on investigating kallistatin levels in liver disease in both human and veterinary medicine, despite the proven sensitivity of this system in liver cirrhosis in both species. The relevance of these research findings extends to both human and veterinary medicine. Novel biomarkers are anticipated to play a crucial role in both the diagnosis and treatment of liver diseases. Furthermore, current research efforts are focused on understanding the effects of kallistatin. Therefore, the objective of this study was to investigate the estimation of kallistatin levels in various subjects and to identify the main factors influencing these parameters.

Kallistatin is a unique biomarker that can be used to predict neurological outcomes in cardiac arrest survivors by assessing neuronal injury.[1] It is thought to be an endogenous protein which synthesized and secreted in liver. Kallistatin has a wide spectrum of biological activities, such as protecting against vascular and organ injury, as well as inhibiting tumor progression. Levels of kallistatin in plasma, body fluids, or tissues are markedly reduced in animal models with hypertension, diabetes mellitus, organ injury, and liver diseases.[2] It is known that protein was first identified in human plasma as a tissue kallikrein-binding protein and as a serine proteinase inhibitor. Kallistatin consists of two structural elements: an active site and a heparin-binding domain, which regulate signaling pathways in the organism.[3] Today, little attention has been given to studies on kallistatin in liver diseases in animals.

The main methods of diagnostic liver diseases of animals

The diagnosis of liver disease in animals is comprehensively conducted through the evaluation of clinical signs and laboratory testing. Liver diseases can be induced by various factors that impact the structure and function of the organ, including infectious, genetic, autoimmune, and metabolic factors.[4] Clinical signs, such as weakness, fatigue, abdominal bloating, pain, and nausea, along with laboratory tests, including blood tests measuring liver enzymes ALT and AST, as well as parameters related to protein and lipid metabolism, are used for diagnosis. Additionally, imaging techniques such as abdominal radiographs, ultrasound, computed tomography, magnetic resonance imaging, and measurements of kallistatin levels are also employed.[5]

Elevations in serum alanine aminotransferase (ALT) and alkaline phosphatase (ALP) are specifically noted in dogs. The measurement of alkaline phosphatase activity exhibits high sensitivity (80%) but lower specificity (50%) for hepatobiliary pathology. However, if the activity of ALP is elevated concurrently with an increase in Glutamine dehydrogenase (GGT) activity in the serum, the specificity for liver disease increases up to 90%.[6] Hepatic enzymes can be categorized into markers of hepatocellular damage and markers of cholestasis. An increase in ALT or aspartate aminotransferase (AST) activity indicates hepatocellular membrane damage in animals.[7] Elevated AST levels in the absence of increased ALT activity may indicate extrahepatic issues, such as muscle injury.[8,9] Elevation of alanine aminotransferase activity in serum is detected for the diagnosis of chronic hepatobiliary disease in canine and feline.[10,11]

Hypoalbuminemia is an insensitive marker for hepatic insufficiency and is only observed in patients with advanced chronic liver disease.[7] In addition to this, serum bilirubin levels can also be used as an indicator to assess liver function. Ultrasonography allows the assessment of the hepatic parenchyma, and biliary tract, and the detection of hepatomegaly and microhepatia. Deficiency in vitamin D levels is associated with the clinical features of chronic liver disease.[9]

Kallistatin as a new biomarker for diagnostic diseases

In addition to the aforementioned methods for diagnosing liver diseases, the exploration of kallistatin as a novel biomarker is currently pertinent.[12] Kallistatin is a plasma protein produced by the liver, that serving to protect organs and cells from inflammation, fibrosis, and oxidative stress.[11] The index of kallistatin serum blood concentrations could help to detection of liver diseases and conduct control loss of liver function during therapy.[12]

The researchers have shown the specificity of kallistatin as an indicator of liver cirrhosis, with respective rates of 64% and 77%. Reduced serum levels of kallistatin correlate with the severity of

cirrhosis, with the lowest levels observed in cases of advanced cirrhosis.[4] According to scientists, significantly reduced levels of kallistatin were recorded in patients with liver disease (7.2±2.5 µg/ml, $p < 0.001$) and sepsis (7.7±3.5 µg/ml, $p < 0.001$).[12] Likely, the decrease in kallistatin levels is directly correlated with liver cell damage, with the most significant decrease observed in patients with liver disease.[10] Similarly, the serum level of kallistatin decreased in patients with liver cirrhosis, with indicators ranging from 7.2±2.7 µg/ml to 4.4±2.2 µg/ml, compared to the control group's level of 8.2±3.5 µg/ml.[12]

Some scientists have also observed a decrease in the levels of this biomarker in patients with acute pneumonia, acute respiratory infections, obesity, and diabetes.[13] Several studies have demonstrated that kallistatin can serve as an effective biomarker for the early detection of liver fibrosis. When combined with biochemical indicators in the blood, this biomarker has shown high sensitivity and specificity in diagnosing chronic liver disease.[14]

The results determined a potential relationship between the levels of kallistatin and the severity of liver injury exposed to carbon tetrachloride (CCl4) in rats. The levels of ALT, AST, LDH (lactate dehydrogenase), GGT, and hematologic findings (white blood cell count, neutrophil count, lymphocyte count, monocyte count) were higher ($P < 0.01$) of rats with liver damage. At the same time, kallistatin was decreased compared to the control group.[15]

The hemoglobin (Hb) levels in the group with severe liver damage were significantly lower ($P < 0.01$) compared to the hematocrit (Hct) and Hb values in the control group. The ELIZA (enzyme-linked immunosorbent assay) method was used to analyze rat serum kallistatin levels.[11,12] Additionally, the level of kallistatin decreased in conjunction with a drop in serum ALT levels in mouse models with liver damage.[13] The effect of kallistatin on survival and organ damage also was studied in mouse models of established sepsis. It was demonstrated that injecting human kallistatin into the mice resulted in attenuating multi-organ injury, inflammation, and mortality in mouse models of polymicrobial infection and endotoxemia.[11,16] These studies prove that kallistatin protein is a sensitive biomarker for this liver pathology and in the future this method will be relevant as an additional diagnostic method.[10,17,18] This method demonstrated the relationship between the severity of liver tissue damage, biochemical and hematological parameters, and the kallistatin levels in the liver of rats.

Conclusion

Various studies consistently support the notion that kallistatin can serve as an effective biomarker for the early detection of liver fibrosis. When combined with biochemical indicators of its functional activity, the measurement of kallistatin levels exhibits greater sensitivity and specificity in diagnosing chronic liver disease. Thus, it can be used as a diagnostic tool for the early stages of liver fibrosis of disease.

At present, the kallistatin system remains inadequately explored in veterinary medicine, necessitating further research and application as an additional diagnostic method for diseases associated with hepatic pathology. This indicator will enable monitoring of recovery progress and assessment of treatment effectiveness, as its decrease directly correlates with the extent of liver cell damage. It will be especially effective for animals with chronic liver disease, in the case of cirrhosis. The determination of kallistatin in blood together with biochemical studies of animals with liver pathology will provide significant diagnostic value.

Acknowledgments

None.

Conflicts of interest

None.

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