Kallistatin and Glypican-3 as Reliable Biomarkers for the Prediction of Liver Cirrhosis

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KEYWORDS
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ABSTRACT
Background: Cirrhosis is a condition in which the liver does not function properly due to long-term damage, this damage is characterized by the replacement of normal liver tissue by scar tissue. Objective: In the present study, an attempt was made to explore the role of kallistatin (KAL) and glypican3 (GPC3) as a predictor of liver cirrhosis (LC) in patients with hepatitis, non-alcoholic fatty acid and autoimmune diseases. Materials and Methods: This case–control study included 98 cirrhotic patients (34 patients with hepatitis B & A, 31 patients with non-alcoholic fatty liver disease and 33 patients with autoimmune) and 30 apparently healthy individuals. The laboratory investigations were performed, and the serum KAL and GPC3 were measured in all volunteers. Results: Serum levels of KAL, GPC3, and TAC were significantly decreased and MDA increased ($p<0.01$) in patients with LC as compared to control. The significant difference can also be indicatly seen in patients with hepatitis > non-alcoholic fatty acid > autoimmune diseases, respectively. The area under the curve (AUC) results obtained indicate that Kal and GPC3 could potentially be used as greater predictive biomarkers in LC with hepatitis > NAFLD > autoimmune diseases (Kal: AUC= -0.97, -0.91, -0.88; Gyp3: AUC= 0.89, 0.84, 0.79, respectively). Conclusion: Incorporating KAL and GPC3 screening into routine check-ups for patients with hepatitis, non-alcoholic fatty liver, and autoimmune diseases could aid in the early detection and prevention of LC-associated complications.

1. Introduction

Liver cirrhosis (LC), the ultimate consequence of chronic liver diseases, is a pathological phenomenon distinguished by widespread hepatic fibrosis, wherein the customary liver structure becomes substituted by regenerating nodules, which can arise from any prolonged hepatic ailment (1). The majority of prevalent incidents of cirrhosis stem from alcohol use disorder (approximately 45% of all cirrhosis cases), hepatitis C (41%), and nonalcoholic fatty liver disease (26%), with a substantial number of patients exhibiting overlapping causes. Nevertheless, hepatitis C can now be remedied through direct-acting antiviral agents, and the majority of recently diagnosed cirrhosis cases are attributable to nonalcoholic fatty liver disease (NAFLD) (accounting for 61.8% of incident cases) and alcohol use disorder (20.0%) (2). The diagnosis of LC patients in resource-limited environments is frequently postponed due to the unavailability of liver biopsy and elastography. The majority of these individuals manifest critical complications that pose a substantial burden on their well-being and lead to increased levels of mortality (3). Kallistatin is a protein of the serpin superfamily of serine protease inhibitors. It is predominantly produced and secreted by the liver. Low concentrations are also secreted by the kidneys, pancreas, heart, arteries, veins, atheroma, blood cells, and bodily fluids. It is an anti-angiogenic, anti-inflammatory, antioxidant, vasodilator, and anti-tumor growth protein. Also, collagen fraction volume, type I and type II collagen expression, and deposition are all decreased by kallistatin (4). Additionally, it prevents the expression of collagen and fibronectin by altering the expression of growth factor-β1 in cultured mesangial cells and reducing the production of reactive oxygen species caused by angiotensin II. Furthermore, due to its ability to block VEGF and bFGF-induced endothelial cell proliferation, migration, and adhesion, kallistatin contributes to the control of tumor growth and angiogenesis (5). Glypican-3 (GPC3), a proteoglycan consisting of heparin sulfate, is strongly expressed in the liver of fetuses but not adults. It is attached to the cell surface by glycosylphosphatidylinositol anchors (GPI). It has been demonstrated that GPC3 and hepatocellular carcinoma (HCC) are tightly connected. According to reports, GPC3 expression can be detected up to 90% of the time in patients with α-fetoprotein (AFP)-negative HCC, indicating that it may be useful for HCC diagnosis (6). To date, a limited number of studies on kallistatin and Glypican-3 in liver diseases of various etiologies has been published, but little attention has been paid to liver cirrhosis. Hence, in the present study, an attempt was made to investigate the relation of kallistatin, glypican3