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REVIEW

Is there a place for serum laminin determination in patients with liver disease and cancer?

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Abstract

Laminin is a glycoprotein which has an important role in the mechanism of fibrogenesis and is, thus, related to hepatic fibrosis in addition to presenting increased levels in several types of neoplasias. However, its determination is not routinely considered in the study of hepatic fibrosis. In this review, the authors critically comment on the role of this glycoprotein compared to other markers of fibrosis through non-invasive procedures (Fibroscan). They also consider its clinical investigational potential and believe that the continuation of these investigations might contribute to a better understanding of the fibrogenic mechanism, which could in turn either lead to the identification of patients at risk of developing fibrosis non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) or at least be used as an indicator for hepatic biopsy in such patients. Finally, the authors believe that serum laminin determination might contribute to the diagnosis of epithelial tumor metastasis and peritoneal carcinomatosis.

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Key words: Laminin; Hepatic fibrosis; Cancer; Cirrhosis; Fibrosis markers

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INTRODUCTION

Laminin was initially identified by TIMPL and MARTIN in 1979[1], from a murine fibrosarcoma, the Engelbreth-Holm-Swan (EHS) tumor. Its molecule is a large complex (approximately 850 kilodaltons) made up of three polypeptidic chains called α1 (with approximately 440 kDa), β1 e γ1 (each one with approximately 200 kDa). These chains are intertwined by disulphide bridges, forming a characteristic cross-shaped asymmetrical structure[1-3].

Laminin is one of the main glycoproteins of the basement membrane and participates in a series of such biological phenomena as adhesion, migration, cellular differentiation and growth, inflammatory response and the maintenance of the cytoskeleton upon its binding to several components of the matrix, such as collagen type IV, heparan-sulphate and entacin[3-7].

Laminin receptors are also found on the surface of a wide range of cells, such as platelets, muscle cells, neutrophils, endothelial cells and hepatocytes[3,6]. Recently, the existence of a class of transmembrane receptors for laminin known as integrins has been demonstrated. These integrins are involved in the mechanisms of cell-cell, cell-matrix and, more recently, pathogen-cell adhesion[3,7,8]. Laminin binding proteins have been described in a number of such pathogenic agents as *Staphylococcus aureus*, *Escherichia coli*, *Helicobacter pylori (H pylori)*, and *Candida albicans*.

LAMININ IN THE LIVER

In normal liver, laminin is found around the vessels and biliary ducts, where basement membranes are identified. Little or only a slight reaction for antibodies against laminin can be observed in the hepatic sinusoids[9,10]. In this organ, glycoprotein is also involved in intracellular activities, such as the normal differentiation of the biliary ducts, genetic expressions for albumin messenger RNA in hepatocyte, and regeneration with normal

lobular organization following partial hepatectomy[11-14]. Laminin is thought to be synthesized by hepatocytes and sinusoidal cells[14,15]. Among all cellular types in the sinusoids, special attention should be given to stellate cells or lipocytes, which produce the largest amount of serum laminin.

With the development of hepatic cirrhosis, laminin and collagen deposition occurs both along the fibers of septal fibrosis and subendothelial sinusoids or Disse's space. At the latter site, laminin deposition, together with collagen deposition, determine the formation of a true basement membrane along sinusoids. This phenomenon is called capillarization of Disse's space[16]. Besides the increased production of laminin in the liver an additional effect due to a lack of degradation of this protein by liver endothelial cells should also be taken into consideration. As demonstrated by Smedsrod *et al*[17] in an experimental model, apart from an increase in tissue deposition or turnover, there would be a decrease in the liver's ability to degrade this protein. With the development of anti-laminin antibodies, directed against the laminin P1 portion, increased levels of this circulating protein were observed in the more advanced stages of fibrosis in patients with hepatic disease[18-22] and as expected these serum levels have a positive correlation with portal pressure[21-26]. Kropf *et al* have proposed laminin serum concentration as a sensitive screening test for hepatic fibrotic disease and portal hypertension, if the test is carried out together with hyaluronic acid determination[21,22]. Laminin as an isolated parameter was found to be highly sensitive, but with low specificity to detect portal pressure above 5 mmHg.

We have assessed laminin serum levels in patients with alcoholic liver cirrhosis and with preserved hepatic function in an attempt to evaluate its predictive value for the risk of variceal bleeding, which is assessed through a portal pressure level equal to or higher than 12 mmHg[26]. In these patients, serum laminin levels were significantly correlated with portal pressure levels (r = 0.70). Such correlation enabled us to find a cut-off level for serum laminin that could correspond more closely to a portal pressure of 12 mmHg, accepted as a threshold for esophageal rupture in those patients. As it was found by others, these laminin levels presented very low specificity and negative predictive values to identify those patients with increased portal hypertension. In fact, patients presenting laminin serum concentration of less than 2.20 U/mL have almost 50% chance of having or not a portal pressure of 12 mmHg or higher.

This low specificity of serum laminin determination in portal hypertension could be related to the fact that laminin levels reflect only structural changes and do not take into account changes in the systemic and portal blood flow, which contribute significantly to portal pressure.

On the other hand, due to the great distribution of laminin in the body's basement membranes, and its limited participation in the liver's extracellular matrix, some issues need to be further investigated and clarified as for the origin of this protein. A study of concentrations of serum laminin in different vascular territories showed that its levels in supra-hepatic veins were higher compared to those found in the renal and femoral veins of patients with fibrosis or hepatic cirrhosis[27], which would be indicative of its hepatic synthesis. Similar findings were also demonstrated in control and carbon tetrachloride treated animals; there was also a significant correlation found between laminin serum levels and the degree of hepatic fibrosis[28] and an important increase was observed in the concentration of this glycoprotein in the supra-hepatic vein when compared to its amount in portal blood[29]. However, the hepatic contribution was much smaller in cirrhotic animals than in those with fibrosis as the sole condition. This fact could point towards decreased hepatic extraction of the protein or an increase in laminin synthesis in other organs of the splanchnic circulation, secondary to the venous congestion of this system. The latter possibility seems to be reinforced by studies with patients infected by *Schistosoma mansoni*. In the hepatosplenic form of the disease portal hypertension is due to periportal fibrosis, which determines pre-sinusoidal portal hypertension with large splenomegaly. Because these patients do not present hepatic cirrhosis, collagenization and capillarization of with Disse's space are not usually found. In these patients, initial studies revealed a significant increase in the levels of circulating laminin, when compared to patients presenting hepatointestinal form and the control group[30-32]. This increase correlated with the levels of portal pressure measured *via* the splenic vein[30, 31]. But, when these patients where submitted to splenectomy, a significantly decrease in the levels of type IV collagen and laminin in the serum of these patients was observed[32]. Since an increased synthesis of basement membrane in the spleen of such patients has been reported, the reduced levels of laminin after splenectomy strongly suggest an important participation of an extra-hepatic source for the serum levels of laminin in these patients[33,34].

Thus, not only might circulating levels of laminin reflect the hepatic processes of synthesis and degradation, but also the increase of the synthesis of basement membranes, as a result of the congestion observed in other splanchnic organs.

Hence, the use of serum laminin as a marker of portal hypertension for clinical use suffers from other extra-hepatic factors which might influence its blood concentration. In addition, recent studies with Fibroscan have found sensitivity and specificity for the diagnosis of portal hypertension in cirrhotic patients far higher than those found through the determination of serum laminin[35,36].

Due to this relationship between laminin tissue deposition and advanced fibrosis, serum levels of laminin have been used by several authors as a non-invasive parameter to assess liver fibrosis in alcoholic patients as well as in those presenting with viral hepatitis and hemochromatosis[37]. Such determination, however, was progressively discontinued as it did not demonstrate to be superior to those of other such components of the extracellular matrix as TIMPs and hyaluronic acid. However,

in recent studies laminin determination has been included in a set of test together with PIIINP, hydroxyproline, prothrombin activity, and AST/ALT in the diagnosis of advanced fibrosis in chronic hepatitis C[35,38-41].

In non-alcoholic fatty liver disease (NAFLD), however, laminin serum levels should be further investigated. In this condition, the fibrogenic stimulus in the perisinusoidal region occurs earlier, with the detection of pericellular and perisinusoidal fibrosis in the early stages of fibrosis[39].

We have more recently been able to assess serum laminin values in NAFLD, and to measure collagen type Ⅳ and hyaluronic acid[42]. Ballooning and hepatic fibrosis in these patients is associated with the progression of the disease[43]. In this preliminary study, we analyzed the discriminative ability of serum laminin, type Ⅳ collagen and hyaluronan and hepatic enzymes levels to predict the presence of fibrosis in 30 overweight patients divided into two groups according to the absence or presence of fibrosis upon liver biopsy. All the three biochemical markers of fibrosis were able to differentiate between these two groups, but laminin presented the best correlation (rs = 0.65) with hepatic fibrosis and the best diagnostic performance, with 87% accuracy. When compared with the BAAT criteria proposed by Ratziu *et al*[44], laminin values presented a better diagnostic accuracy for the diagnosis of septal fibrosis (83% × 70%) and for the presence of any fibrosis.

Although laminin was not evaluated, in a study with 112 patients with NAFLD, 70 of whom with at least grade 1 fibrosis, Sakugawa *et al*[38] were able to confirm our findings that hyaluronic acid and type Ⅳ collagen were useful in discriminating the patients with fibrosis from those with steatosis only. The subtle differences in diagnostic accuracy performance for these biochemical markers of liver fibrosis found in our study and that by Sakugawa *et al*[38] might be attributable to the fact that their study included a higher number of patients with any given degree of fibrosis (62% × 37%) or advanced fibrosis (37% × 10%). On the other hand, Lydatakis *et al*[36] showed that HA determination was more useful in the diagnosis of fibrosis than serum laminin and type Ⅳ collagen. No correlation was observed among laminin level and the grade of hepatic fibrosis, possibly due to the method and patients selection. It's important to take into account the small number of studies on fibrosis markers by indirect method.

In studies by Sakugawa *et al*[38] HA serum levels have been well demonstrated to significantly increase in cirrhotic patients when compared to the other degrees of fibrosis. In this manner, the determination of serum laminin values can not only play a useful role in the identification of NAFLD patients with a certain degree of fibrosis, but also in the distinction between patients with simple steatosis and those with non-alcoholic steatohepatitis (NASH) and a certain degree of fibrosis. Finally, the determination of serum laminin values might become a selection parameter of patients for the indication of fibrosis. A study bearing this purpose is currently being conducted in our laboratories.

SERUM LAMININ IN NEOPLASTIC DISEASES

Not only have serum laminin levels been studied in patients with liver diseases, but also in patients with cancer, especially in cases where tumor proliferation and invasion are found. Serum values tend to increase significantly with the emergence of metastases, irrespective of tumor lineage or the organ originating the neoplasm[45-48].

Hence, serum laminin could be regarded as a tumoral marker in cases of alterations in the basement membrane, proliferation and tumoral invasion[48]. In fact serum laminin concentration is increased in metastatic cancer of different origins as melanoma, gastric adenocarcinoma, hepatocellular carcinoma, colorectal cancer, epithelial ovarian tumor[49-52].

Grounded on these observations and the findings by Byers *et al*[53] and Chu *et al*[54], who observed increased concentrations of laminin in the ascites of metastatic breast tumors, we decided to study the discriminative ability for this glycoprotein in serum and in ascites to (differentiate) discriminate between ascites due to peritoneal carcinomatosis and hepatic cirrhotics[55]. By using polyclonal antibodies against laminin isolated from human placenta, a significant increase in serum and ascitic laminin levels was observed in patients with peritoneal carcinomatosis when compared to patients with hepatic cirrhosis with or without hepatocellular carcinoma.

Although immunohistochemical studies have shown important laminin deposition in cases of neoplastic transformation of hepatocytes[56,57] and despite the considerable representation of the group of patients with HCC once they presented advanced disease with large tumor masses with high serum alpha-fetoprotein levels, blood and ascites laminin values did not distinguish these patients from those with liver cirrhosis without tumor complication. In benign and malignant ascites, serum laminin values were higher and showed excellent correlation with its value in the ascitic fluid (r = 0.93, P < 0.0001). Thus, these findings indicated that serum laminin levels can also be a marker of neoplastic ascites. Indeed serum laminin showed high discriminative ability for the diagnosis of malignant ascites, with 75% sensitivity, 100% specificity and 91% accuracy[43].

So, considering the potential of laminin for clinical investigation, it seems to us that more studies are needed in order to clarify if there are still a place for serum laminin determination in the diagnosis of hepatic fibrosis in NAFLD and in the diagnosis of epithelial tumors metastasis and peritoneal carcinomatosis.

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