Lipoprotein(a) as a potential marker of residual liver function in hepatocellular carcinoma

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ABSTRACT

The residual liver function is a major clinical index in hepatocellular carcinoma (HCC) patients. As the liver plays a crucial role in lipid and lipoprotein metabolism, the significant impairment of the hepatic function occurring during chronic liver diseases, such as HCC, can influence plasma lipoprotein profiles. Although, lipoprotein(a) (Lp(a)) circulating concentrations are mostly determined by genetic factors, in the majority of reports they have shown a correlation with the hepatic status and a significant decrease in HCC and liver cirrhosis patients than among the controls. In such a way, Lp(a) may represent a new additional and useful marker for a more complete assessment and monitoring of the liver function in patients with HCC and liver cirrhosis. Further studies are needed in order to evaluate the clinical significance of Lp(a) in HCC.

Key words: *Chronic liver disease, hepatocellular carcinoma, liver function, lipoprotein(a)*

INTRODUCTION

The liver carries out important biochemical duties on endogenous and exogenous substances including drugs.[1] Therefore, liver function integrity is essential to maintain a physiological metabolism of carbohydrates, lipids, and amino acids.[2,3] Lipids are insoluble in water, thus they are carried along the plasma with proteins.[4] Most lipids are transported in lipoprotein complexes through the bloodstream.[5] Lipoproteins are globular, high-molecular-weight particles consisting of a core which contains non-polar lipids, triglycerides, and cholesterol esters, and surrounded by a polar surface coat, made of a single layer of phospholipids, unesterified cholesterol, and specific proteins, the so-called apolipoproteins.[4-7] Apolipoproteins, which are synthesized by liver and gut, are expressed on the surface of lipoproteins and, besides ensuring the structural stability, they influence lipoprotein metabolism by activating specific enzymes and binding to cellular receptors.[8] Since the liver plays a crucial role in lipid and lipoprotein metabolism, the significant impairment of the hepatic function occurring during chronic liver diseases, including hepatocellular carcinoma (HCC), can influence plasma lipid profiles.[3] HCC is a challenging malignancy of global importance and is associated with a high rate of mortality. Nowadays, HCC is representing the fifth most common cancer all over the world and the third most frequent cause of mortality amongst oncological patients. It is responsible for more than 500 000 deaths with over 600 000 new worldwide cases yearly.[9,10] More than 95% of patients with HCC have an underlying chronic liver disease which is most often associated with virus hepatitis B and C.[11] HCC is now the leading cause of death among cirrhotic patients.[12] Cirrhosis is an independent risk factor for the onset of HCC.[13] The best pathogenetic hypothesis points out a process with several stages. In this process, mature hepatocytes acquire further genetic alterations in a microenvironment where the coexistence of hepatic necrosis, inflammation and regeneration leads to the selection of monoclonal populations and the formation of dysplastic nodules.[14,15] The staging systems for HCC take into account the severity of concomitant liver disease and the degree of the residual liver function, which are major conditioning elements for prognosis. The systems so far proposed to measure the liver function are not fully accepted by everyone, therefore the research is still aimed

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at developing new methods of measurement. A greater number of reports on HCC have shown abnormal plasma patterns of lipids and lipoproteins.[3,16-18] This review is focused on the pathophysiological significance and the clinical impact given by fluctuations in lipoprotein(a) (Lp(a)) plasma levels observed during HCC.

LIPOPROTEIN(A): A SUIS GENERIS MOLECULE

Lipoprotein(a), also called Lp(a), is a lipoprotein subclass; it is a "suis generis" molecule consisting of a low-density lipoprotein (LDL)-like particle whose apoB-100 is covalently bound to the apoprotein(a) (apo(a)) through a disulfide bridge. It was first described more than 40 years ago by Berg[19] though it still looks like a mysterious molecule, as its physiological role has not been revealed yet. There is an analogy between the apo(a) and the plasminogen genes: they both have coding sequences for loop structures, stabilized by intrachain disulfide bonds, the so-called kringle (K) domains.[20] Apo(a) contains 10 distinct subclasses of plasminogen kringle IV-like domains (KIV1−KIV10). While apo(a) KIV types 1 and 3−10 are present as single copies, the kringle IV type 2 domain (KIV2) is present in a variable number of identically repeated copies and it is the molecular basis for the observed isoform size heterogeneity of Lp(a).[21] The heterogeneity of apo(a) explains a large fraction of the variability of plasma Lp(a) concentrations, and there is a clear negative correlation between the molecular weight of apo(a) and the plasma Lp(a) concentration.[22-24] The two main Lp(a) subunits, apo(a) and apoB-100, are independently processed and released by the liver to form covalent particles within the extracellular compartment. The final assembly of Lp(a) occurs trough a two-step mechanism where a noncovalent interaction between apo(a) and apoB-100 precedes the disulfide linkage formation.[25] Lp(a) catabolism still remains unclear, but there is evidence against a great involvement of LDL receptors in this process.[26] The most widely used methods to measure Lp(a) in the clinical laboratory are the commercially available immunoassays (immunoturbidimetric analysis and ELISA method).[27] Lp(a) plasma levels are extremely variable among individuals, from less than 0.2 to more than 200 mg/dl, and their distribution does not follow a Gaussian type curve. Approximately 90% of the population have serum Lp(a) values lower than 300 mg/L though values above 20000 mg/L have occasionally been found.[23] Although Lp(a) circulating concentrations are mostly determined by genetic factors,[21] they may display more or less significant fluctuations, under different physiological and pathological situations or pharmacological agents. Lp(a) levels in postmenopausal women are higher than in premenopausal and perimenopausal women.[28] Lp(a) serum levels are decreased in subjects with liver failure [16,29] or hyperthyroidism.[30] Mink *et al.*[31] reported that Lp(a) concentrations were significantly higher among the acute phase response patients (infections, postoperative, tumors, and other diseases) than among the controls. The clinical interest around Lp(a) largely springs from the recognition of it as a cardiovascular risk factor. Although it is not counted among the major traditional risk factors, increased Lp(a) levels have shown a correlation with cardiovascular disease in several studies.[32-34] Moreover, recent data indicate that Lp(a) is a cardiovascular risk factor independent of traditional ones, such as LDL cholesterol, low HDL cholesterol levels, hypertension, diabetes mellitus, obesity, sedentary, and smoking.[35,36] In some cancer types, apart from HCC, Lp(a) plasma levels have been found to be elevated, but in general few data are still available about Lp(a) concentrations in cancer patients.[37]

RELATIONSHIP BETWEEN LP(A), HEPATIC STATUS, AND HCC

Since the majority of HCCs occur in patients with liver cirrhosis, the evaluation of the liver function plays a central role in the fields of therapeutic decision, tumor staging, and prognosis.[38] Liver function can be assessed readily by routine laboratory tests (alanine and aspartate aminotransferase, albumin and bilirubin serum levels, prothrombin and international normalized ratio (INR) values, platelet and white cell counts, blood ammonia level, ferritin), but several factors make the changes in concentration of this analytes difficult to interpret when considered individually.[39] The Child-Pugh classification has incorporated some of these routine laboratory tests, representing thus the first systematic approach to determine the index of the residual liver function.[40] However, it is based on some subjective parameters such as ascites and encephalopathy that make the assessment less accurate.[41] The model for end-stage liver disease (MELD) score, which includes the international normalized ratio (INR) and serum bilirubin and creatinine levels in the calculation, has recently emerged as a very valuable method for the assessment of residual liver function. MELD score has been shown to have significant advantages in clinical practice, especially in those patients who are candidates for liver transplantation.[42,43] However, it is greatly criticized in some respects. For example, serum creatinine levels and INR show significant discrepancies using different laboratory methodologies.[44,45] Several studies have reported that the addition of other prognostic factors to those evaluated by MELD score may increase accuracy in evaluating liver function and prognosis.[46-48] Other methods of liver function estimation, based on the principle of clearance of substrate by the liver, have been developed. The substrates

include indocyanin green, lidocaine, galactose, aminopyrine aminoacid, and methacetin. There are also tests based on the principle of energy production by the liver, such as arterial ketone body ratio and AKBR, and others based on the number of receptors for asialoglycoprotein (ASGP-R; technetium-99m-galactosyl human serum albumin; 99mTc-GSA scan). Nevertheless, an accurate, yet practical and cost-effective method of liver function evaluation has not been clearly defined.[49]

The liver is the main site of lipoprotein synthesis.[50] The formation of lipoproteins is a complex and gradual process that begins in the rough endoplasmic reticulum where apolipoproteins are synthesized. In the smooth endoplasmic reticulum, the various lipid fractions link to apolipoproteins. After that, the newly formed lipoproteins get to the tanks of Golgi apparatus where they buy the carbohydrate component required for their secretion. The liver also plays a central role in lipid metabolism. The modification and disposal of the lipid material depends on the liver which can send the circulating lipid material in the form of ketone bodies, triglycerides, phospholipids, and cholesterol, the three last ones being linked to lipoproteins.[7,51-54]

The liver is the cardinal organ for Lp(a) synthesis.[55] Apo(a) is synthesized by the hepatocytes as a low molecular mass precursor, and then modified in the endoplasmic reticulum and transferred in the Golgi apparatus.[56] It is unclear if the final assembly of Lp(a) takes place inside or outside the cell, probably on the hepatocyte surface, and from there Lp(a) is released into the circulation.[57] Several studies have shown an association between Lp(a) plasma levels and chronic liver diseases. Lp(a) levels decrease as the disease progresses.[16,55,58] It has been demonstrated that serum Lp(a) levels in patients with chronic liver diseases, induced by hepatitis viral infections, are significantly reduced when compared to healthy controls.[16,55,58-60] Malaguarnera *et al.*[55] reported a significant increase of Lp(a) levels occurring after the treatment in patients with chronic active hepatitis C. Only patients who responded fully presented a significant increase in the values of Lp(a). These findings suggest that increased levels of Lp(a) represent an expression of improved liver function. Since the liver is the organ that synthesizes Lp(a), reduced level of Lp(a) during chronic liver diseases may be attributed to the relative decrease in the synthesis by a damaged liver. In the course of HCC and/or cirrhosis, circulating Lp(a) have displayed abnormal patterns.[16,55,58,60] Thus, it is conceivable that the status of hepatic cellular impairments, various cytokines delivered during the disease, and hormone environment may influence the metabolic pathway of Lp(a).[16] Lp(a) plasma levels are influenced early when liver function is impaired, because the half-life of Lp(a) is about 3.3-3.9 days in human plasma.[61,62] Lp(a) plasma levels, at variance with the other lipoproteins, are not affected by dietary changes.[63] While Basili *et al.*[64] found elevated levels of Lp(a) in HCC patients, in three different case control studies Lp(a) plasma levels showed a significant decrease in patients with HCC and liver cirrhosis than among the controls.[16,58,60] Moreover, Motta *et al.*[16] noticed a significant negative correlation between Lp(a) and Child-Pugh degrees, α-fetoprotein and ferritin values as well as a positive one with albumin and cholinesterase levels calling for a role of Lp(a) as a marker of liver disease also in HCC.

CONCLUSIONS

With its complexity, Lp(a) could act as a marker of residual liver function. Its structure is indeed an expression of lipid (LDL-like particle) and protein (apoB-100) metabolism, and of coagulation state (apo(a)) as well. Since in the overall population Lp(a) blood concentrations are extremely variable from a subject to another, cohort studies would be more appropriate than case control studies at evaluating the relationship between Lp(a) and HCC. In such a way, it would be possible to evaluate the fluctuations of Lp(a) levels over time, with serial measurements with the progression of the disease and the consequent deterioration of the liver function. The presence of HBV or HCV infection, generalized inflammatory state or other conditions could be confounding factors though they have not been analyzed separately in any study. Lp(a) may supply useful additional information for a more complete assessment and monitoring of the liver function in patients with HCC and liver cirrhosis. Further investigations are needed in order to verify Lp(a) accuracy at measuring the residual liver function in HCC patients, especially in comparison with other methods of liver function evaluation.

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