INCREASE OF GLYCOSAMINOGLYCANS AND METALLOPROTEINASES 2 AND 9 IN LIVER EXTRACELLULAR MATRIX ON EARLY STAGES OF EXTRAHEPATIC CHOLESTASIS

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Common endpoint for most types of chronic hepatic injury is substitution of liver parenchyma by scar tissue, causing fibrosis, considered an irreversible process. Extrahepatic cholestasis (EC) produces hepatocellular injury, leukocyte infiltration, epithelial biliary cells proliferation and fibrosis of liver parenchyma by extracellular matrix (ECM) replacement. The aim of this work was to evaluate liver ECM changes on extrahepatic cholestasis induced by bile duct ligation, analyzing glycosaminoglycans content and matrix metalloproteinase (MMPs) activities. Wistar rats (6-8 weeks; n = 40) were submitted to bile duct ligation and euthanized 2, 7 or 14 days after surgery, with sham-operated animals used as control. Disease evolution was analyzed by body and liver weight, seric direct bilirubin, globulins, gamma glutamyl transpeptidase (GGT), alkaline phosphatase (Alk-P), alanine and aspartate aminotransferases (ALT and AST), tissue myeloperoxidase and MMP-9, pro MMP-2 and MMP-2 activities, histopathology and glycosaminoglycans content. Cholestasis caused cellular damage with increase on globulins levels and GGT, Alk-P, ALT and AST activities. There was neutrophil infiltration observed by the increasing of myeloperoxidase activity on 7 (P = 0.0064) and 14 (P = 0.0002) groups which leads to the magnification of tissue injuries. Bile duct ligation increased pro-MMP-2 (P = 0.0667), MMP-2 (P = 0.0003) and MMP-9 (P<0.0001) activities on 14 days, thus indicating matrix remodeling and establishment of inflammatory process. Bile duct ligation animals showed an increase on dermatan sulfate and/or heparan sulfate content reflecting extracellular matrix production and growing mitosis due to parenchyma depletion. Cholestasis led to many changes on rats’ liver parenchyma, as so as on its extracellular matrix, with major alterations on MMPs activities and glycosaminoglycans content. This work shows that the whole process of tissue depletion after bile salts accumulation ends up increasing MMPs activity, which leads to inflammation and ECM renovation, causing tissue fibrosis with major changes on GAGs content.

Keywords: Extrahepatic cholestasis. Glycosaminoglycans. Matrix metalloproteinases.
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