Karolinska Institutet

Institutionen för Medicin, Solna

NON-ALCOHOLIC FATTY LIVER DISEASE
An emerging liver disease

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Medicinsalen A6:04, Karolinska Universitetssjukhuset, Solna

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av
Cecilia Söderberg
Master of Science

Huvudhandledare:
Professor Rolf Hultcrantz
Karolinska Institutet
Institutionen för Medicin, Huddinge

Bihandledare:
Docent Per Stål
Karolinska Institutet
Institutionen för Medicin, Huddinge

Fakultetsopponent:
Docent Fredrik Rorsman
Uppsala Universitet
Institutionen för Medicinska Vetenskaper
Enheten för Klinisk Kemi

Betygsnämnd:
Professor Mikael Björnstedt
Karolinska Institutet
Institutionen för Laboratoriemedicin
Enheten för Klinisk Patologi och Cytologi

Docent Paolo Parini
Karolinska Institutet
Institutionen för Laboratoriemedicin
Avdelningen för Klinisk Kemi

Docent Stergios Kechagias
Linköpings Universitet
Institutionen för Klinisk och Experimentell Medicin
Enheten för Gastroenterologi och Hepatologi

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ABSTRACT

The aim of the study was to evaluate what NAFLD is from a molecular perspective, what influences the disease progression and what the prognosis of the disease is.
Fatty liver has earlier often been associated with excessive alcohol intake and only in the last two decades has it been viewed as a condition in non-drinkers i.e. non-alcoholic fatty liver disease (NAFLD). Nowadays NAFLD is considered the most common cause of liver disease, showing that this is a highly modern problem that has taken epidemic forms. NAFLD is strongly associated with obesity, insulin resistance/diabetes, atherosclerosis and hypertension, thus NAFLD is considered the liver's manifestation to the metabolic syndrome. NAFLD encompasses a wide range of clinical diagnosis from simple steatosis to non-alcoholic steatohepatitis (NASH) and cirrhosis to, in some individuals, hepatocellular carcinoma (HCC).

In the first study we investigated the mortality and causes of death in a cohort of subjects with elevated serum levels of aminotransaminases. We determined the frequency of NAFLD and NASH in this population and compared the survival rate and the causes of death in NAFLD-subjects to those subjects with other liver diseases, and to the general population of Sweden. NAFLD was detected in 118 subjects of the total 256, 51 out of the 118 subjects were classified as NASH. During the follow-up period 47 (40%) of the 118 subjects diagnosed with NAFLD died. Compared with the total Swedish population, subjects with NAFLD exhibited 69% increased mortality and subjects with NASH, an increased risk with 86% and NAFLD-patients tend to in a higher extent die form liver disease.

Hyperferritinemia is quite common in NAFLD patients and in the second study we used two animal models of hepatic steatosis to investigate how iron regulatory genes are affected by steatosis alone or in combination with increased oxidative stress and inflammation. We found an increased hamp1 expression in leptin deficient *ob/ob* mice and it seems to be caused by up-regulation of the IL-6, STAT3, Hamp1-pathway, indicating systemic inflammation. Hepatocytes from both NAFLD mice-models were more sensitive to oxidative stress than their non fat controls.

In the third study, we evaluated biopsies from 31 NASH or borderline NASH subjects. We saw that in livers with NASH, hepatocytes with microvesicular steatosis seem to express more inflammatory markers, and in these livers an increased number of Foxp3+ T-cells (e.g. regulatory T-cells) and increased area of CD68 cells were seen. NASH patients also showed positive staining for inter cellular adhesion molecule-1 (ICAM-1) on hepatocytes and that it was localized in areas with microvesicular fat. ICAM-1 was also found to be increased in the blood circulation of NASH patients.

In the fourth study, we evaluated the role of neural cell adhesion molecule (N-CAM) in biliary type fibrosis and liver fibrosis due to parenchymatous disease. N-CAM knock out mice had attenuated liver fibrosis after bile duct ligation but not after carbon tetrachloride injections. Furthermore, hepatic stellate cells isolated from N-CAM knock-outs had impaired activation. These results suggest a role of N-CAM in biliary type liver fibrosis.

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