UNIVERSITY OF MEDICINE AND PHARMACY TÂRGU-MUREŞ
FACULTY OF MEDICINE

Abstract

PhD Student: Szalman Krisztina

Scientific Advisor: Prof. Brassai Zoltan

THE COMPLEXITY OF CLINICAL AND PARACLINICAL INTERFERENCE IN NONALCOHOLIC FATTY LIVER DISEASE

Introduction

Nonalcoholic fatty liver disease (NAFLD), the hepatic manifestation of the metabolic syndrome, is currently the most common chronic liver disease in the world. The prevalence of NAFLD is high, exceeding 30% in some countries, and it is growing continuously. The pathogenesis of NAFLD is complex, closely related to insulin resistance, which is a key element in the pathogenesis of NAFLD. NAFLD further increases the insulin resistance, thereby a vicious circle constitutes. Evolution of NAFLD is unpredictable, it is estimated that approximately 6-10% of cases have a progressive evolution to cirrhosis. The severity of liver disease can't be estimated by simple diagnostic methods, diagnose is based on liver histology, which can be assessed only by liver biopsy or expensive laboratory methods validated for noninvasive assessment of the type and severity of histological changes in the liver.

NAFLD is closely linked to atherosclerosis, most patients with NAFLD exhibit many metabolic risk factors of atherosclerosis. Nature of this relationship is subject of research, it is assumed that NAFLD might be an independent risk factor for atherosclerosis in addition to the risk posed by the elements of the metabolic syndrome.

The main reasons for choosing NAFLD as the subiect of this thesis were the actuality of the NAFLD in hepatology and the complexity of its relations with cardiovascular diseases. This thesis consists of two chapters. The first chapter is dedicated to NAFLD, presenting the theoretical aspects of this disease, from its definition, epidemiological data, pathogenesis and pathology to the diagnostic methods and therapeutic principles. We highlighted the importance of NAFLD, which became the epidemic of hepatology in the 21st century.

The second chapter presents our personal research, it consists of two different studies. The aim of the first study was to assess the epidemiology of NAFLD, the relationship of certain laboratory parameters with liver ultrasound. It also evaluated the role of NAFLD as an independent or associated risk factor for peripheral vascular diseases. The second study aimed to identify some simple noninvasive diagnostic methods that could be useful in selecting patients with potentially severe forms of NAFLD, requiring precise diagnose and propper treatment and follow-up.

Study nr. 1 - *Research on the epidemiological aspects, laboratory and ultrasonographic features of the liver in nonalcoholic fatty liver disease and its correlation with peripheral vascular diseases*

The retrospective study included a total number of 1943 patients admitted to our clinic between July 2008 and April 2010. We selected three subgroups of patients, according to the presence of the following conditions:

- NAFLD, diagnosis of this condition was made based on well- established positive and exclusion criteria
- peripheral arterial disease (PAD), diagnosed on clinical symptoms and signs and CW-Doppler or echo Doppler examination
- primary venous thromboembolism (VTE), the presence of deep venous thrombosis being confirmed by echo Doppler examination, and all cases of secondary VTE being excluded

The NAFLD group consisted of 398 patients, representing 20.5% of all patients. The severity of steatosis appreciated by ultrasound correlated significantly with male gender, serum triglycerides and serum gammaglutamiltransferase (GGT) value. Prehepatic diameter was higher in those with type 2 diabetes, and it correlated with the GGT-value.

The PAD group included 426 patients (21.9% of all patients). Patients were divided according to the presence of NAFLD in two subgroups. Distribution on different age groups was influenced by the presence of NAFLD, patients associating NAFLD with PAD were on average 10 years younger than those with PAD without NAFLD. Estimated risk (Odds ratio) for developing PAD under the age of 65 years was 1.58 fold higher in patients with NAFLD, compared to those without NAFLD. NAFLD was associated risk factor for PAD in patients with type 2 diabetes mellitus and in case of hypertriglyceridemia.

The third group included 101 patients with primary VTE (5.2%). We found a two fold higher prevalence of primary VTE (11.5%) in those with NAFLD compared to the prevalence of primary VTE in all patients admitted to our clinic. Also, NAFLD was over two times more common among patients with primary VTE than in all patients admitted to our Clinic. OR for VTE was 3.54 among patients with NAFLD, compared to those without NAFLD. NAFLD also increased the risk of VTE if associated with obesity, type 2 diabetes or hypercholesterolemia.

Conclusion: The prevalence of NAFLD was 20.5% in our patients. This prevalence is approximately 30% lower than in the United States or other countries with the highest prevalence, exceeding 30%. Male gender, increased serum GGT and hypertriglyceridemia were the most simple clinical and laboratory parameters predictive of severe steatosis. NAFLD increased the risk of PAD if combined with other risk factors of the metabolic syndrome. It represented an independent risk factor for VTE, and associated with obesity, it multiplied the risk of VTE.

Study nr. 2. *Correlations of liver histology with anthropometric and laboratory parameters in nonalcoholic fatty liver disease*

39 patients with metabolic syndrome diagnosed according to the IDF criteria and histologically proven NAFLD were included in this study. Histological scoring was made in each case, after the Brunt model, evaluating the grade of necroinflammatory activity and the fibrosis stage. We analyzed the correlation between anthropometric and laboratory parameters, the insulin resistance quantified by the HOMA- IR modell, the APRI (AST to platelet ratio) index and the NAFLD histological score.

The grade of necroinflammatory activity was minimal in half of the cases, and only 12.5% of cases were found with grade 3 necroinflammatory activity. Fibrosis stage was minimal or intermediate in most cases.

Interferential statistical analysis revealed positive correlation between necroinflammatory activity and body mass index, waist circumference, blood glucose, serum triglyceride and cholesterol levels. This correlation was significant only in case of the serum GPT value. Fibrosis severity correlated with serum triglyceride and cholesterol levels. We found statistically significant correlation between the presence of type 2 diabetes and the fibrosis stage. The correlation between the APRI index and the stage of fibrosis was statistically significant, with p 0.0001, except for stages 1 and 2. These stages were associated with very close APRI values. The HOMA-IR correlated with both histological parameters, but multiple comparison performed by Tukey test revealed statistically significant correlation between HOMA-IR and necroinflammatory activity only for grades 1 and 2.

Conclusion: In NAFLD, histologically mild forms are more prevalent. Severity of liver histology can not be assessed with appropiate sensitivity on antromethric or laboratory parameters defining metabolic syndrome. An APRI index value above 1.3 in NAFLD is highly suggestive for the presence of cirrhosis, but it does not provide adequate information about the fibrosis severity in case of minimal and intermediate stages of fibrosis. The HOMA- index is a not a usefull tool for assessing NAFLD severity.