

**Mini Review**

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Non-Alcohol Fatty Liver Disease Goes Beyond the Liver

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Non-alcohol fatty liver disease is not only a liver disease but also an important driver in a metabolic disease entity that effects many extrahepatic organs. It is attributing to the development and aggravation of diabetes, cardiovascular diseases and cancer. The change to a hypercaloric, sedentary, lifestyle is the basis of this fast-growing problem. It diagnostic and therapeutic approach is far beyond the liver disease and needs a multidisciplinary, multifactorial approach starting with awareness.

Keywords: Non-alcohol; Fatty liver disease; Non-alcoholic steatohepatitis; Metabolic syndrome; Insulin resistance.

Abbreviations: NAFLD: Non-Alcohol Fatty Liver Disease; NASH: Non-Alcoholic Steatohepatitis; HCC: Hepatocellular Carcinoma; CVD: Cardiovascular Disease

Introduction

The liver is a multitasking organ with a large reserve capacity. It plays a crucial role in metabolic homeostasis. Progressive steatosis will compromise different liver functions and can lead to severe organ dysfunction when the functional demand is increased as for example in sepsis.

In physiological situations, the functional volume of the liver is adapted to body need. The liver enlarges when the capacity of hepatocytes is stressed like for example in progressive steatosis. In non-alcohol fatty liver disease (NAFLD) fat accumulation is greater than 5% in combination with well-defined alcohol intake (men a maximum of 20 grams and women 10 grams ethanol per day). To date, NAFLD is the new challenge as HCV infections will be eradicated with the effective drugs that have been developed over the years. About 25% of the world population [1] is somewhere in the spectrum of: simple steatosis, non-alcoholic steatohepatitis (NASH), NASH with fibrosis progressing to severe complicated liver disease and hepatocellular carcinoma (HCC).

Multiple hits are responsible for the disease progression; some persons are more susceptible to get severe NAFLD. About one third of persons with a steatotic liver develop into complicated liver disease between 10 to 30 years. Does that mean that the health of the other two third is not affected by the steatosis? This is probably

not true as the liver plays also a key function in the interaction with other extra hepatic organs.

Discussion

The liver functions as a sieve with its specific, unique, fenestrated endothelium. It is the first station in the metabolic process after gastrointestinal absorption of proteins and carbohydrates, entering via the portal vein. Lipids are mainly absorbed by micelle formation transported via the lymphatic system entering the central circulation and transported to the liver for metabolism. A dysfunctional liver filter function could affect the clearance of toxic lipids that take part in atherosclerosis. The hypercaloric diets, characteristic of the Western way of life, causes accumulation of energy in the form of fat mainly localized in the abdominal compartment and the liver. At a certain point insulin resistance is induced that in the end lead to pancreatic exhausting. NAFLD is part of the metabolic disturbance in the, each other influencing factor, pathogenic circle of overweight, obesity, diabetes and cardiovascular diseases with characteristics of the metabolic syndrome. Therefore, a metabolic healthy liver will have an effect on general health.

To date, it is still difficult to predict who will develop a NAFLD related liver disease and who other complications. Although, with common sense, it is possible to do case finding in your practice. For a

person with unhealthy diet, alcohol and nicotine abuse, overweight and obesity, little physical activity in a background of familial cardiometabolic diseases it is quite easy to predict the outcome. The majority of persons are not that classic in presentation therefore a more advanced diagnostic armamentarium is needed.

Diagnostic approach

Different non-invasive methods are being developed to help to find the patient that is in a more advanced liver disease stage. The liver biopsy as the gold standard is not a useful tool to screen patients with suspected NASH. It is a necessity when the differential diagnostic with other chronic liver diseases has to be ruled out like for example auto immune hepatitis. But high costs, side effects and the aversion of patients for this invasive diagnostic makes it difficult to be used on large scales. Therefore, a lot of effort is put in finding the combination of non-invasive techniques to diagnose and follow the clinical progression or regression of NAFLD.

NAFLD a systemic disease

Interestingly, the majority of persons with NAFLD do not present with an overt liver disease but with cardiovascular diseases (CVD), complicated diabetes or cancer [2]. That means that the metabolic changes attribute to systemic diseases. In 2015 we organized our first European Fatty Liver conference (ELFC) focusing on the systemic effects of NAFLD [3]. We stated that NAFLD is a systemic, progressive disease. Today, it is a commonly accepted concept that NAFLD is part of a metabolic systemic disease that has insulin resistance as an important pathogenic factor.

It has been shown that NAFLD with progressive liver fibrosis is an independent factor in the disease severity of CVD, diabetes and the development of all sorts of cancers [4]. This gives evidence to the fact that the chronic liver inflammation is strongly related to systemic inflammation. The low grade chronic systemic inflammation is a silent killer that takes many years to harm.

Risk profile

Finding the person at risk is the new task for health care providers. Today many algorithms are being used to stratify the disease severity and to calculate the risk to develop certain diseases. It seems likely that a specific risk profile should be developed for NAFLD to predict which person will be at risk to develop progressive liver disease and/or its systemic complications. In the near future, it will probably possible, with the aid of big data, that risk profiles can be combined into one cardio-liver-metabolic profile to be calculated with an app.

Future perspective

The next step will be to convince the person to change his way of life to prevent the development of chronic metabolic diseases. This is another challenge as changing behavior is quite difficult. Programs for losing weight are proven not to be that successful for the long run. For a short period, patients are willing to take a diet that has a rapid effect on losing weight as for example before bariatric surgery, taking a low caloric crash diet. It helps to degrease the liver and omental fat depot, facilitating the surgeon to perform a laparoscopic bariatric operation more easily. However, diets and

physical activity, as the cornerstone of a healthier lifestyle, are still difficult to prolong as a new habit. Eating patterns are difficult to change because it is not only a habit that is influenced by family tradition but is even more severely influenced by external factors. Western societies are exposed to unhealthy consuming; at the street by fast processed foods, caloric beverages and alcohol that are also advertised in all sorts of manners like on TV and in newspapers. It is difficult to withstand this influence and young children are often not aware of the danger of overheating and high caloric snacks. As tobacco advertising is nearly abolished, the next step is alcohol and thereafter it will be unhealthy obesogenic food. It will take some time but at a certain point we have to introduce barriers for the food industries to stop advertising that what lead to chronic metabolic diseases. This will become part of preventive strategies to halt the increase in overweight, obesity and diabetic. It is a necessary way to go, as healthcare costs are increasing due to the unhealthy Western way of life. The ideal world is not in reach yet but we are being forced to change our way of life. The first step is awareness for the individual that by a healthy norm caloric diet and physical activity a prolonged disease-free life can be achieved. This has to be supported by governmental prevention programs. The alimentary industries also have to take responsibility for producing and advertising healthy food.

Conclusion

NAFLD can lead to a chronic liver disease as well as a low-grade systemic inflammation affecting different extra hepatic organs. A multidisciplinary approach in diagnostic and therapy will be the challenge to battle this slowly progressive disease entity that goes far beyond the liver. The first step is awareness supported by scientific evidence that changing life style is essential. Each individual has its own responsibility in preventing NAFLD and its complications. However, an important task is given to the authorities to develop preventive programs and the food industry to produce and advertise healthy nutrition. There is still a long way to go.

Acknowledgement

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Conflict of Interest

No Conflict of Interest.

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