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Inactivity and fatty liver disease

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Abstract

Physical activity represents a key element in the prevention and management of many chronic diseases. On other hand physical inactivity is a primary cause of obesity, metabolic syndrome and nonalcoholic liver disease. A higher body weight is associated with an increased incidence of a number of conditions, including diabetes mellitus, cardiovascular disease and nonalcoholic fatty liver disease. Obesity is associated with a increased risk of all-cause mortality. Hepatic consequence of sedentary lifestyle is nonalcoholic fatty liver disease (NAFLD), which is now in Western countries the most common cause of chronic liver disease. NAFLD primary affects hepatic structure and function. NAFLD cause morbidity and mortality from liver cirrhosis, liver failure and hepatocellular carcinoma. The majority of deaths

among NAFLD patients are attributable to cardiovascular disease (CVD) and cancer. NAFLD is strongly associated with the clinical features of insulin resistance and is the hepatic component of metabolic syndrome.

Keywords: inactivity, obesity, metabolic syndrome, nonalcoholic fatty liver disease

Introduction

Obesity is a growing epidemic worldwide with a significant burden on healthcare utilization. Between 1980 and 2004, the prevalence of obesity increased from 15% to 33% among adults in the United States.[1] Obesity, defined by a body mass index (BMI) of 30 kg m−2 or more, has been associated with adverse health events, increased mortality and a substantial economic effect. Obesity accounts for nearly 10% of US healthcare expenditures and an estimated 300 000 individuals die each year of weight-related disease.[2] Despite the numerous complications associated with obesity, previous reports have yielded conflicting results regarding mortality of obese patients in the acute hospital setting. Obesity is a well-established risk factor for non-alcoholic fatty liver disease (NAFLD), leading to cirrhosis in a subset of patients.[3] In addition, obesity as a widespread condition may coexist with advanced liver diseases of other aetiologies. While obesity has been linked to higher probability of clinical decompensation in patients with cirrhosis.[4]

Nonalcoholic liver disease (NAFLD)

Obesity is a global epidemic contributing to an increasing prevalence of obesity-related systemic disorders. Several studies have reported the alarming increase in obesity and metabolic syndrome in Western countries. One recent large population-based study in the United States, utilizing data from the National Health and Nutrition Examination Surveys from 2009-2010 (NHANES), reported obesity rates of 35 %.[1] With the increasing epidemic prevalence of obesity, diabetes, and the metabolic syndrome in the general population is increasing prevalence of NAFLD.[3] Nonalcoholic fatty liver disease is now the most commom hepatic disease in the Western world. The rising prevalence of NAFLD globally may be accounted for by changes in dietary habits and an increase in sedentary lifestyle. Prevalence is high and there is a trend towards a further increase, with millions of people at risk of advanced liver disease. The risk of development of NAFLD increase with numbers of

components of metabolic syndrome. Up to 70% patients with type 2 diabetes mellitus have NAFLD. The prevalence of hepatic steatosis (NAFL) in general population in Western countries is cca. 30-35%.[5] At the other end of the distribution, data on the prevalence of NAFLD among high-risk individuals with severe obesity have become widely published. 76% of the patients undergoing bariatric surgery have steatosis, 37-70% have NASH, 30% fibrosis, and up to 10% liver cirrhosis.[6], [7]

Type 2 diabetes mellitus, obesity and dyslipidemia are the principal factors associated with NAFLD, which is now considered the hepatic expression of metabolic syndrome.[8] The epidemics of diabesity of Western countries is expected to produce a significant increase of NAFLD in the next years. NAFLD today has become an importand cause of liver cirhhosis, liver failure and hepatocellular carcinoma. Mortality among diagnosed NAFLD patients is higher than the general population.[9] Three leading causes of death in patients with nonalcoholic fatty liver disease (NAFLD) are cardiovascular disease, cancer, and liver disease. Prevention and intervention programs based on lifestyle are therefore mandatory to reduce the burden of liver disease.

Pathogenesis of NAFLD

Insulin resistance is the common pathogenic event linking obesity, type 2 dia- betes mellitus, hypertension, endothelial dysfunction, dyslipoproteinemia with fatty liver disease. The accumulation of fat dropelets in hepatic parenchyma is the backround of NAFLD. This proces is driven by several factors synergistically. The patogenesis of NAFLD appears to be multifactorial, involving external enviromental factors, behavioral and genetic factors. Main factors contributing to NAFLD are diet (calorie dense foods), inactivity, genetic factors and endotoxemia from gut microbiota[10].

The presence of unhealthy livestyle factors, physical inactivity and high calories intake leading to massive enlargement adipose tissue and insulin resistence are expected to increase the lipid depots in the liver. The gut microbiota may also be involved. Obesity, insulin resistance, hepatic inflamation are generated and perpetuated via gut-derived toxic factors. Several data support a primary role of genetic factors. A few gene polymorphisms are associated with risk of nonalcoholic fatty liver disease development and progresion to advanced liver disease and hepatocellular carcinoma.

Natural history of NAFLD

Nonalcoholic fatty liver disease includes a spectrum of liver disease that ranges from simple fat accumulation (simple steatosis) in the liver to cellular damage-necroinflammation (steatohepatitis-NASH), fibrosis, cirrhosis, and hepatocellular carcinoma. These spectrum represent all the stages of the natural history of NAFLD. Simple steatosis is generally a mild and stable disease whereas NASH can be progressive. The progression from NAFL to NASH is currently being studied, whereas the progression of NASH to cirrhosis and HCC has been well established.

Progression from steatosis to steatohepatitis.

Only a minority of NAFLD patients progress to significant fibrosis. In general, it is thought that fibrosis progression in patients with NAFL is uncommon, whereas NASH progresses more rapidly and frequently. NAFL (simple steatosis) can evolve to NASH with advanced fibrosis, which would imply that it may not be an entirely benign condition.[11] Recent study has found 44% of the patients with NAFL progressed to NASH and 37% had progression of fibrosis, including 22% to advanced fibrosis.[12]

Progression from steatohepatitis to cirrhosis.

Progression of steatohepatitis to advanced fibrosis and cirrhosis has been well documented in several studies. A metaanalysis that included seven NASH studies noted that 34 % of patients developed progressive fibrosis, 39% remained stable, and 27% had improvement in fibrosis.[13]

Progression of cirrhosis.

Natural history is characterized by an asymptomatic phase, termed "compensated cirrhosis" followed by a progressive phase marked by the development of complications of cirhhosis, termed "decompensated cirrhosis." With the progression of the NAFLD portal pressure increases and liver function declines, resulting in complications such as ascites, variceal bleeding, encephalopathy and jaundice. Development of any of these complications heralds the transition from a compensated to a decompensated cirhosis. Transition from a compensated to a decompensated stage occurs at a rate of approximately 5 to 7% per year.[14]

Progression to hepatocellular carcinoma.

Progression from NASH to cirrhosis increases the risk of progression to HCC. HCC is now a major cause of mortality in NASH patients.[15] The rising problem is, that nonalcoholic fatty liver disease with or without NASH can predispose to HCC in the

absence of cirrhosis or advanced fibrosis. NAFLD associated HCC in the absence of cirrhosis raises the important question of HCC screening for this risk group.[16]

Extrahepatic consequences

NAFLD typically exists in a milieu of disturbed metabolism, including increased total body adiposity, insulin resistance, impaired glucose tolerance and dyslipidemia. Hepatic lipid accumulation in NAFLD impairs hepatic glucose and lipid metabolism further increasing the risk of type 2 diabetes mellitus and of cardiovascular disease. It is not surprising that CVD is the leading cause of death in NAFLD patients. NAFLD is an important and independent risk factor for the development of atherosclerosis and therefore CVD.[17] The normal glucose and lipid homeostasis within the liver becomes disturbed with the accumulation of hepatic fat, resulting in hepatic insulin resistance, increased fasting glucose levels and an atherogenic lipid profile. Moreover, weight gain in NAFLD subjects exacerbates the adverse cardiovascular risk. The fatty liver is also a producer of a number of inflammatory proatherogenic cytokines, hypercoagulable factors and adhesion molecules, which have been implicated in the pathogenesis of atherosclerosis and myocardial dysfunction.[18]

There are many risk factors that influence the natural history of NAFLD. Nonalcoholic fatty liver disease has been reported to be significantly higher in elderly people. Obesity is increasing in adults and also in children. NAFLD is strongly linked to obesity, with a reported prevalence as high as 80% in obese patients. Both a personal and family history of diabetes increases the risk of NASH and fibrosis among patients with NAFLD. The presence of diabetes has long-term prognostic significance in patients with liver disease because it is an independent predictor of cirrhosis and HCC.[19] The severity of NAFLD intensifies with lower physical fitness. Several observational studies have shown correlations between fitness or sedentary behavior and the risk NAFLD and NASH.[20] Visceral adiposity seems to be a major determinant of the correlation between fitness and exercise habits and NAFLD. The presence of NAFLD was predicted inversely by fitness and directly by BMI.[21] Diet high in carbohydrates might worsen the clinical conditions of patients with NAFLD. Patients with NAFLD often have a high-fat diet that may be an independent risk factor for the development of NASH.[22] The quality of fats plays a key role in the pathogenesis of NAFLD as shown by the beneficial effect of monounsaturated fatty acids, and polyunsaturated fatty acids.[23]

Treatment of NAFLD

The consequence of our physiology is the adaptation to new living conditions. Evolution selected for organisms which are able to store energy for survive famine. Nowadays we dont need to be extremly physicaly acive to find and get food. We are constantly exposed to high energy and high caloric nutrients. Weight loss improves liver tests. Corelation between weight changes and transaminases activity was found.[24] Patientns who gained more than 5% of body weight saw an improvement in their transaminases. This weight reductioun was associated with decrease in serum triglycerides and fasting blood glucose level, HDL cholesterol increase as well as blood pressure reduction. Losing of 5% body weight was enough to improve insulin resistance as well as steatosis. Loss of 9% of body weight was associatet with regresion of liver steatosis, reduction of inflamation in the liver histology.[25] Regression and histologic improvement of NASH and fibrosis have been documented also after bariatric surgery. Bariatric surgery induced the disappearance of NASH from nearly 85% of patients.[26]

Physical activity reduses steatosis of the liver of patients with NAFLD. Even when it is not enough to change body weight or to improve ALT level.[27], [28] Obese men with physical activity of more than 4 hours per week had improvement of liver steatosis and also improvement of hepatic stiffnes.[29] Demonstrated decrease in liver fat and improvement of insulin sensitivity is the benefit of Mediteranean diet with high consumption of monounsaturated fatty acids.

Fructose in sweetened sodas reduces the satiety sensation, it is taken up to to hepatocytes where it increase lipogenesis as well as the production of reactive oxygen species. Fructose promote fibrosis and inflamation in the liver.[30]

There are more and more data showing beneficial effects of coffee. Regular coffee intake may have a protective role against NAFLD.[31] It is clear that the first approach for patients with NAFLD/NASH is to change their habits and improve lifestyle.

Antioxidative medication is discussed as a medication for NAFLD/NASH. Vitamin E treatment can improve hepatic steatosis. Ursodeoxycholic acid and obeticholic acid are bile acids that can improve liver steatosis. Treatment with bile acid is associated with significant reduction in liver tests. Obeticholic acid treatment was also associated with weight reduction. There are more drugs on the pipeline in the group of trancription factors (elafibranor) or caspase inhibitors (emricasan). The target is regresion or resolution of hepatic fibrosis.

Role of Inactivity

The population burden of inactivity is unacceptably high. Physical inactivity has been identified as one of the biggest public health problems of the 21st century.

Crucial importance of physical activity is undervalued and underappreciated by many individuals in public health and also health workers. The typical physician is many times more likely to measure cholesterol, blood pressure, and BMI than to measure fitness. Physicians and other clinicians could at least take a physical activity history and put physical activity on the patient's agenda.[32]

Definitions for exercise, physical activity do not include a definition of "physical inactivity". Logical definition of physical inactivity is a lack of sufficient physical activity to maintain a healthy balanced lifestyle for prevention of premature death. Regular physical activity represents a key element in the prevention and management of many chronic diseases. Othervise physical inactivity is a primary cause of obesity and associated metabolic disorders. Direct consequence of sedentary and excessive lifestyle is NAFLD.

Physical inactivity is now identified as common risk factor for global mortality (WHO, 2010). Physical inactivity levels are rising in many countries with major implications for increases in the prevalence of noncommunicable diseases and the general health of the population worldwide.[33]

Epidemiology of Inactivity in Slovakia

Epidemiologic analysis of life style factors of liver outpatient in Slovakia was an national, out-patient based cross-sectional study over Slovakia. Data were collected through the uniform anonymous questionnaire filled in in waiting rooms of clinic by patients before their examination. In Slovakia in population aged 15 years and over were insufficiently active, our screening detected physical inactivity in very high proportion, in 68 % of patients.

There is a need for strategy, that attack children and young people in an acceptable and atractive way. We need to discover strategies and therapeutic methods appealing to willpower, but in equally sophisticated way such as factors of inactivity do (PC, videogames, electronical devices). Understanding the barriers to physical activity and creating strategies to overcome them may help make physical activity part of new healthy lifestyle. Successfully changing our sedentary society into an active one will require effective dissemination and acceptance of the message that moderate physical activity confers health benefits. The public health community will need global action

plan if improvement in population levels of physical activity is to occur. Schools and the medical community are specifically targeted because they offer the means to reach most of population. Physicians and other health professionals should routinely counsel patients to adopt and maintain regular physical activity. Physicians can be effective proponents because patients respect, physicians and the frequency with which Americans visit them suggest that even modestly effective physician counseling would have a substantial public health impact.[34]

About one-third of adults worldwide do not reach for recommended levels of physical activity. One of the approaches to increase PA is through primary health care. However, providing only verbal advice has proven to be insufficient.[35]

The most effective strategy is medical/professional advice, repeated visits and guidance with continued support and behavior change strategies.[36],[37] Schools should deliver comprehensive health and physical education programs that provide and promote physical activity at every opportunity. Parents should be physical activity role models for their children and support their children's participation in enjoyable atractive physical activities. Political leaders and city planners have the power to improve population health and equity by pursuing healthy and sustainable urban design.

Conclusions

Obesity=globesity is a growing epidemic worldwide with a significant burden. Physical inactivity is one of the most important public health problems of the 21st century with hepatic consequence - nonalcoholic liver disease. Physical activity is a fundamental means of improving physical health. Two thirds of the adult population in the European Union and Slovakia do not reach recommended levels of activity. Society is responsible for creating conditions that can facilitate active lifestyle. Promoting physical activity should be seen as a necessity. Action should be complex. Countries, regions and cyties need to reverse the trend towards inactivity and create conditions for making physical activity part of everyday life. Action should be large-scale, coherent and consistent across different levels of government and different sectors.

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