Austin Journal of Obesity & Metabolic Syndrome

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Austin Publishing Group

Short Communication

Non-Alcoholic Fatty Liver Disease - Hepatic Manifestation of Obesity

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Received: October 10, 2018; **Accepted:** October 24, 2018; **Published:** October 31, 2018

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Non-Alcoholic Fatty Liver Disease (NAFLD) is the most common chronic liver disease and will become number one high risk factor for development of hepatocellular carcinoma. Rising prevalence of NAFLD is anticipated with the rise in prevalence of obesity. Prevalence of NAFLD could be as high as 90% among obese individuals. Well-known risk factors for development of NAFLD are obesity, T2DM, dyslipidemia, hypertriglyceridemia, hypertension and history of cyclic weight gain and loss.

Clinical spectrum of NAFLD ranges from simple steatosis to nonalcoholic steatohepatitis (NASH). Steatosis is the hallmark of NAFLD that occurs due to increased uptake of hepatic fatty acid from plasma. Altered adipose tissue lipolysis, regional hepatic lipolysis of circulating TG and tissue FFA transport proteins are involved in the pathogenesis of ectopic accumulation fat leading to steatosis. Liver ultrasound, liver function tests and history of alcohol intake help to diagnose NAFLD. Accumulation of type and distribution of packing of fat is key issue in the development of NAFLD.

NAFLD, the most common underlying risk factor for HCC is present in 90% of obese and 70% of T2DM individuals and plays key role in development of hepatocellular carcinoma. There is complex interplay among different pathophysiological pathways and genetic and environmental factors for development of NAFLD related HCC. NAFLD is now considered as the hepatic manifestation of metabolic syndrome. Parallel increase in prevalence of obesity and NAFLD will be major challenging issue in forthcoming decades.

Introduction

NAFLD is now recognized as the most frequent cause of chronic liver diseases associated with overweight and obesity. Now it is considered as the hepatic manifestation of metabolic syndrome. It is characterized by an Increase in Intrahepatic Triglyceride (IHTG) content (steatosis) with or without inflammation and fibrosis (steatohepatitis) in the absence of other causes for secondary fat accumulation in liver like alcoholism, hereditary conditions or use of steatogenic agents [1]. Its prevalence has raised to more than 30% of adults in general population in developed countries. The estimated prevalence of NASH among adults in general population is 2-3 % and up to 35% among morbidly obese population [2,3]. NAFLD is the most common chronic liver disease and will become number one high risk factor for development of HCC [4]. Rising prevalence of NAFLD is anticipated with the rise in prevalence of obesity.

Obesity and NAFLD

Obesity has been identified as independent risk factors for NAFLD. As the prevalence of obesity is rising at rapid pace, prevalence of NAFLD is increasing dramatically worldwide. Prevalence of NAFLD could be as high as 90% among obese individuals [2]. It has become an important public health issue because of its progression to severe liver disease and association with serious cardio-metabolic abnormalities [5]. Exact prevalence of NAFLD is still underestimated because of the differences in the study population and modalities used for diagnosis of NAFLD. But it increases with increasing Body Mass Index (BMI). A large population based study reported presence of steatosis by sonography among 91% of obese individuals (BMI>30kg/m^2) [6]. Well-known risk factors for development of NAFLD are obesity, T2DM, dyslipidemia, hypertriglyceridemia, hypertension and history of cyclic weight gain and loss. Even though metabolic syndrome is found to be closely associated with NAFLD, the metabolic syndrome is now recognized as strong predictor of the presence of NAFLD [7]. T2DM and insulin resistance are independent risk factors for NAFLD and chronic liver diseases related mortality.

Mechanistic connection between obesity and NAFLD

Clinical spectrum of NAFLD ranges from simple steatosis to Non-Alcoholic Steatohepatitis (NASH). Simple steatosis may have benign clinical course, but NASH can progress to fibrosis, cirrhosis and Hepatocellular Carcinoma (HCC) [8]. Steatosis is defined chemically when Intrahepatic Triglycerides (IHTG) content more than 5% of liver volume or liver weight or histologically defined when 5% or more of hepatocytes contain visible intracellular TG [9,10]. Steatosis is the hallmark of NAFLD that occurs due to increased uptake of hepatic fatty acid from plasma. Also de nova synthesis of fatty acid is more than rate of oxidation of fatty acids and excretion. So steatosis develops when the rate of FA input is more than its rate of output. Thus there is complex interplay of different metabolic reactions of fatty acids, which affect glucose and lipoprotein metabolism also. Altered adipose tissue lipolysis, regional hepatic lipolysis of circulating TG and tissue FFA transport proteins are involved in the pathogenesis of ectopic accumulation fat leading to steatosis [5]. Steatosis has 3% lifetime risk of progression to cirrhosis, while 20% of the cases with NASH can develop cirrhosis over a period of 10 years [11].

Strong association of NAFLD is found with components of metabolic syndrome including obesity and Type 2 diabetes mellitus (T2DM) has components of metabolic syndrome. Most of NAFLD patients Excessive IHTG is obese people is a robust marker of various metabolic abnormalities like insulin resistance in liver, muscle and

Citation: Takalkar UV and Nageshwar DR. Non-Alcoholic Fatty Liver Disease - Hepatic Manifestation of Obesity. Austin J Obes & Metab Synd. 2018; 3(1): 1010.

adipose tissue, altered metabolism of FFA and increased secretion of very low density lipoprotein and TG [5]. Liver ultrasound, liver function tests and history of alcohol intake help to diagnose NAFLD. Sedentary lifestyle led to obesity, metabolic syndrome and cardio metabolic complications at a much younger age. Overnutrition associated with obesity result in insulin resistance that is an invariable attribute of NAFLD. Asma Deeb et al reported fatty liver as the frequent condition in overweight and obese children and adolescents with elevated transaminases. They found strong association of waist circumference with dyslipidemia and fatty liver in the studied population [12].

Visceral fat releases Free Fatty Acids (FFA), and adipokines and exposes liver to accumulation of fat. Accumulation of fat causes liver lipotoxicity. Accumulation of type and distribution of packing of fat is key issue in the development of NAFLD. Lipotoxic mediators responsible for this condition are free cholesterol, saturated fatty acids, diacylglycerols, lysophosphatidyl-choline, sphingolipids and ceramides. Lipid toxicity kills hepatocytes by apoptosis, necrosis, necroptosis and pyroptosis that lead to mitochondrial injury, oxidative stress, innate immune response and inflammatory response [13]. NAFLD, the most common underlying risk factor for HCC is present in 90% of obese and 70% of T2DM individuals and plays key role in development of hepatocellular carcinoma. There is complex interplay among different pathophysiological pathways and genetic and environmental factors for development of NAFLD related HCC [14].

Jakobsen MU and colleagues reviewed results of 24 studies to evaluate association of abdominal fat content by waist circumference and imaging methods with fatty liver. They concluded direct association between abdominal fat and liver fat content that is accounted by visceral fat. Presence of metabolic syndrome carried a high risk of NASH (OR, 3.5; 95%CI, 1.2-8.9; p=0.26) and severe fibrosis (OR, 3.5; 95%CI, 1.1-11.2; p=0.32) among NAFLD subjects [15,16].

Epidemic of obesity is coupled with presence of different components of metabolic syndrome, which is a major burden for forthcoming liver failure in future. NAFLD is now considered as the hepatic manifestation of metabolic syndrome. There is accumulation of neutral fay chiefly TG in liver in the absence of significant ethanol consumption, viral infection or other specific etiologies due to imbalance between lipid availability and disposal. It triggers lipoperoxides stress and hepatic injury landing up to further complications [17].

Presence of NASH and fibrosis in liver is considered as high risk factor for development of liver and cardiac-related morbidity and mortality. Although obesity is a common clinical phenotype associated with NAFLD and different components of metabolic syndrome, but not all-obese person develop NAFLD and it can be found among non-obese subjects also, especially in children and adults of all ethnicities, more common among Asians. Estimated prevalence of NAFLD among non-obese subjects varies from 3-30 % in different populations. Visceral adiposity, excess intake of cholesterol, fructose, genetic risk factors and state of low-grade insulin resistance has been identified to be associated with NAFLD among non-obese persons. Among such individuals distribution of fat is more important than total body fat content [18]. Growing parallel epidemic of obesity and metabolic syndrome need to acknowledge as a major worldwide public health cancer. Data suggest a very strong correlation between NAFLD and metabolic syndrome, insulin resistance being a common factor.

Conclusion

Parallel increase in prevalence of obesity and NAFLD will be major challenging issue in forthcoming decades. HCC has been linked to NAFLD, a major hepatic manifestation of overweight and obesity and related metabolic conditions. Hence prevention of obesity with therapeutic lifestyle change is the cornerstone for prevention of NAFLD and related complications. Although absolute risk of HCC associated with NAFLD is low, rising global prevalence of obesity and NAFLD will be staggering.

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