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Community Medicine

PREVENTIVE ASPECT OF NONALCOHOLIC FATTY LIVER DISEASE IN INDIA - A MODERN EPIDEMIC

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ABSTRACT Nonalcoholic fatty liver disease (NAFLD) has become very prevalent these days and due to its association with the modern type of lifestyle, it can rightly be said as a modern epidemic. The key factor in the causation of NAFLD is the insulin resistance. It may be considered a part of the metabolic syndrome characterized by diabetes mellitus, hypertension, and obesity. The objective of this article is to study the risk factors associated with the pathogenesis of NAFLD and modification of those risk factors to prevent this condition at primary and secondary levels. Sedentary living, lack of exercise, high fat and sucrose diet, high saturated fat and low omega-3 fatty acid in the diet, low fiber diet, stress and strain, irregular sleep pattern and environmental pollutions are known environmental and behavioral factors related with NAFLD. Besides these, some metabolic factors associated are obesity, insulin resistance, and diabetes, hypertension, and hyperlipidemia. Prevention of NAFLD depends upon modification of these modifiable factors. Control of obesity (especially childhood obesity), regular exercise, healthy dietary habits, and a safe environment are helpful in primary as well as secondary prevention. Some drugs are also being used to prevent the progression of the disease.

KEYWORDS : Nonalcoholic Fatty Liver Disease (NAFLD), Nonalcoholic Steatohepatitis (NASH), Insulin Resistance (IR), Metabolic Syndrome (MS).

INTRODUCTION:

In the last two centuries the world has passed through four epidemiological stages: 1) Age of Pestilence and Pandemics 2) Age of Receding Pandemics 3) Age of degenerative manmade diseases and 4) Age of delayed degenerative diseases. And now it has passed into the fifth stage i.e. stage of inactivity and obesity.[1] This change in the pattern of diseases is more obvious in western countries where change is homogenous and the whole society passes from one stage to other at the same time. No part in the World is unaffected from this epidemiological transition caused by industrialization, urbanization, and change in the lifestyle and diet. However, in developing countries, people of all stages can be seen in the same society at the same time. Main features of the modern living are increasing inactivity and a high-calorie diet. Therefore Incidence and prevalence of Chronic Non-communicable diseases, cardiovascular diseases, diabetes, cancers have increased unprecedentedly. [2] These are now modern epidemics. One of the modern epidemics is the Nonalcoholic fatty liver disease (NAFLD).

NAFLD has now become an important cause of liver disease in India. The prevalence of NAFLD in India varies from 9 to 30% in the different parts of the country as reported by different studies done here.[3] It can be compared with the western countries where its prevalence is reported to be about 25 to 30% of the population with higher estimate {74%} among obese.[4]

NAFLD encompasses a spectrum of hepatic pathology with different prognosis. Initial end of the spectrum includes simple accumulation of triglycerides in the liver cells (hepatic steatosis) and on the opposite extreme end is cirrhosis liver as well as primary liver cancer and in between stage is Non-Alcoholic Steatohepatitis (NASH).

Normal Liver – Hepatic steatosis—NASH—Cirrhosis of liver--- Liver cancer. [5]

NAFLD is strongly associated with obesity/overweight and insulin resistance but it can also occur in lean individuals. Ethnic or racial factors also appear to influence liver fat accumulation. Other factors which are associated with the NAFLD are viral, amoebic or other hepatitis, injury to hepatocytes by drugs or toxins and congenital diseases. NASH is a heterogeneous condition. At times it may remain stable for years or may improve to steatosis while sometimes it deteriorates to progressive accumulation of fibrous scar leading to cirrhosis of the liver. [6,7]

In the United States, population-based abdominal imaging studies have shown that the prevalence of NAFLD is 25% in the American adult population. NASH is present in about 25% of individuals who have NAFLD. Advanced fibrosis or cirrhosis may develop in 25% of people suffering from NASH. Thus it may be concluded that 6% of individuals with NAFLD may develop cirrhosis in their life. At the same time, it is also clear that 1.5-2% individuals of the general population will develop cirrhosis of the liver due to NAFLD. The situation is very similar in India in middle and high socioeconomic group of people.

Hepatitis C related cirrhosis of the liver is the major indication of liver transplantation in the world. However, the experts predict that very soon NFALD related cirrhosis will become the most common indication of liver transplantation. This trend can be understood clearly in the USA, where the prevalence of cirrhosis due to Hepatitis is 0.5% and prevalence due to NAFLD is 3 to 4 times higher than this. [7]

NAFLD is also related to intrahepatic cholangiocarcinoma (ICC) and hepatocellular carcinoma with or without cirrhosis of the liver. Thus NAFLD may also be considered as a premalignant condition.[8]

NAFLD is not limited to adults only but it is also found in children. Rising prevalence of childhood obesity indicates that it may become a major cause of childhood morbidity in the coming future if proper preventive measures are not adopted.[9]

The epidemic of NAFLD, NASH, and cirrhosis related to it has erupted in India like a modern epidemic. Besides rising number of Obesity, Insulin Resistance and Diabetes in India other factors like sedentary lifestyle, the diet rich in fat and sugar and low in fibers, various stress and strain, Infections, drugs, and environmental pollutions have a great impact on the eruption of this modern epidemic. Therefore effective preventive measures and health education must be adapted to control and prevent this health problem.

LITERATURE REVIEW:

To meet the above objectives literature search was performed with the help of electronic databases and printed journals related to pathophysiology, etiology, prevalence, diagnosis, prevention and treatment patterns of NAFLD/NASH. The search yielded many relevant articles whose full texts were retrieved, evaluated, summarized and this review article was prepared.

Non-alcoholic Fatty Liver Disease (NAFLD) was first described by Ludwig and colleagues in 1980. Other terminologies used for this disease at that time were pseudo-alcoholic hepatitis, alcohol-like hepatitis, nonalcoholic Laennec's disease, fatty liver hepatitis, diabetic hepatitis, and steatonecrosis.[10] Though pathological pictures of this disease resemble that of alcohol-induced liver disease, it occurs in patients who do not abuse alcohol. Now NAFLD is used to describe a wide spectrum of fatty liver diseases ranging from simple steatosis (fat accumulation without any change in hepatocytes) at one end to NASH (fat accumulation, change in hepatocytes, inflammation and possibly some fibrosis) and its complications (cirrhosis of the liver and hepatocellular carcinoma) at the other end. [11]

Although liver biopsy is the gold standard for the diagnosis and staging of NAFLD, it is an invasive procedure and is not acceptable at the community level. Therefore most of the epidemiological studies are done on the basis of imaging methods to calculate the prevalence of NAFLD. Prevalence of NAFLD was found to vary from 8% to 30% in the general population in the different studies done in Asian countries during the year 2002 to 2012. Similar studies done in North America showed that the prevalence of NAFLD in the general population varied from 13% to 18% whereas the prevalence of NASH varied from 2% to 4%. No gender variation was found but ethnic variation was found. It was less common in African Americans as compared to European Americans and Hispanic Americans.[12]

NAFLD is a part of metabolic syndrome. It is mostly associated with other components of metabolic syndrome as obesity, diabetes, and dyslipidemia. In Asian studies, the prevalence of NAFLD was found to vary from 15 to 80% in obese people and 25 to 60% in dyslipidemias. Abnormal glucose tolerance is directly related with the NAFLD and its prevalence increases in parallel with the progressive degree of impaired glucose tolerance. In one study the prevalence of fatty liver was 33% in prediabetics and 55% in diabetes patients in India. In another study in India, it was shown that the prevalence of NAFLD in diabetics vary from 57% to 64%. In 2011 Sanal et al did a study in India and found that 42% of patients of NAFLD had metabolic syndrome. [13] Similarly in a study in Malaysia prevalence of NAFLD was found to be 56% in people with hypercholesterolemia. Prevalence of NAFLD increases with the degree of obesity.[14] A 2009-10 study from Japan showed that prevalence of NAFLD increased linearly with the increasing BMI, with BMI less than 23 kg/sqm having a prevalence of 10% while BMI more than 28 kg/sqm having a prevalence of 84%.[15]

A number of studies have shown that NASH underlies up to two-thirds of 'cryptogenic cirrhosis'. Similar results were found in different studies done by Indians, Duseja et al[16] and Amarapurkar et al[17] and a study done in Japan by Sakugawa et al.[18]

Children are a very important part of the population from the prevention point of view. An increase in childhood obesity is leading to an increase in the number of NAFLD in childhood. A cross-sectional study in India showed that children aged 5-12 years had 3% prevalence of NAFLD .[9,19] Similar results were found in some studies of Japan and Korea.

Although NAFLD can occur at any age the prevalence increases with the age. Most Asian studies showed that it is most common in the 4th and 5th decade of life. [16] Development of insulin resistance with increasing age may be one reason for it. The gender difference is not clear. In some studies, it was seen that prevalence was less in women during the premenopausal period.

A high-fat diet can lead to steatosis by causing obesity and insulin resistance, however, hepatic steatosis can develop without peripheral insulin resistance with conditions that cause a localized alteration in hepatic fat and glucose metabolism. Increase in a dietary fatty acid pool can cause accumulation of fat in the liver independent of peripheral insulin resistance. However, some studies have shown that high-fat feeding cause over nutrition and intrahepatic fat accumulation only if concomitant carbohydrate ingestion is high. Rather than quantity, qualitative composition of fat is a matter of more concern. Consumption of saturated fats predisposes to the development of NAFLD while polyunsaturated fatty acids (PUFA) are protective. Among the PUFAs only omega-3 fatty acids are protective (not omega-6 fatty acids). Patients with NAFLD have been found to consume less omega-3 fatty acids. Other studies have found that excess carbohydrate is more responsible for NAFLD than fat consumption (especially fructose intake). Fructose is taken up entirely by liver unlike glucose and since it cannot make glycogen it stimulates lipogenesis and inhibits beta-oxidation. It not only worsens hepatic steatosis but also leads to an increase in triglyceride-rich VLDL particle formation which is taken by skeletal muscle leading to muscular IR. [20]

Several observational studies have found that patients with NAFLD are less physically fit than controls. They do less physical exercise and lead an inactive life. Interventional studies have shown that physical exercise both aerobic and non-aerobic reduce steatosis similar to the effects of a hypocaloric diet and the benefit is independent of weight loss. [21]

Development of liver injury, from steatosis to steatohepatitis and fibrosis, has many theories. There is no relation between the amount of steatosis and degree of inflammation, and all patients with steatosis do not progress to develop steatohepatitis and fibrosis. Theory of 'two-hit' was given initially, in which it was proposed that the first hit is 'steatosis' and the second hit is gut-derived endotoxin which produces 'inflammation' and condition progresses to NASH. However, recent data suggest that NASH seems to be a disease of 'three hits' or even multiple hits acting in parallel including lipotoxicity, oxidative stress, mitochondrial dysfunction, and inflammatory cytokines.[22]

DISCUSSION:

Nonalcoholic Fatty Liver Disease (NAFLD) has become a modern epidemic all over the World including India. In a very short period there is a tremendous rise in its incidence and prevalence and now it has become a leading cause of liver disorders including cirrhosis of the liver and hepatocellular carcinoma. Very soon it will become the leading indication of liver transplantation.

NAFLD is mainly a disease of modern lifestyle, however, there is a definite role in the genetic composition. It clusters in families, with the heritability of NAFLD being estimated to be 39%.[23]Several genes are found to be associated with NAFLD. Gene mapping can be an important tool for risk assessment in the future.

Weight loss- Weight loss has a definite role in the improvement of steatosis and steatohepatitis. In a study, there was a histological improvement in 9 out of 15 persons after an average loss of 3 kg for one year. So weight loss is one of the most effective strategies to reverse a fatty change in hepatocytes. It can be achieved by diet control, exercise, use of weight loss drugs or bariatric surgery. Majority of obese persons have NAFLD (57-74%) and NASH (15-20%) compared to 10-24% and 3-4% respectively in the general population. Obesity also predisposes to insulin resistance. General obesity, central obesity, and visceral obesity are independent risk factors. Central obesity and visceral obesity contribute more to IR than general obesity.[24]

Diet Control- Low-calorie diet, especially low in sucrose and saturated fat content has a definite role in the improvement of liver inflammation, liver enzymes, and insulin resistance. Lipid and carbohydrate provide substrates for hepatic liver synthesis as well as activate SREBP-1 and ChREBP transcription factors. In one study it was seen that for an average 8% reduction in weight with the low-fat diet (1200 kcal), there was an 80% reduction in intrahepatic lipid content as well as the reduction in hepatic triglyceride content, fasting plasma glucose, and total cholesterol. Whole body insulin sensitivity also improved. However ketogenic diets have demonstrated greater weight loss and better lipid profile than the low-fat diet. This type of diet in NAFLD patients led to a significant improvement in hepatic steatosis, inflammation, and fibrosis. In another study, it was seen that diet rich in omega-3 fatty acid led to improvement in NAFLD.[25]

Physical Exercise – Physical exercise can be applied as a mode of intervention at every level of prevention of NAFLD. It is seen that NAFLD is less common in physically active persons doing regular exercises. It is seen that vigorous exercise (both aerobic and non-aerobic reduces) not only reduces steatosis but is also associated with lower risk of fibrosis even after the appearance of the disease. A beneficial effect of physical exercise in this condition is not only direct but also indirect, by reducing bodyweight and decreasing insulin resistance. [26]

Insulin Resistance- Insulin resistance is the key factor in the development of steatosis due to its important action on skeletal muscle, fat cells and the liver, i.e., on all important organs of lipid and sugar metabolism. Insulin resistance is an almost universal phenomenon in the patient with NAFLD, including lean patients without obvious glucose intolerance. Prevalence of IR in patients with NAFLD was found to be 63-98% in various studies. Prevalence of NAFLD in diabetic patients is very high (about 70-74%) as found in some studies, but the prevalence of diabetes in NAFLD patients is not so high; it is about 12-14%. However, over the years many patients with NAFLD do develop frank diabetes. Now, NAFLD is considered an integral part of a metabolic syndrome, which is becoming very common these days. Metabolic syndrome (MS) characterized by the presence of many metabolic abnormalities (at least 3 out of 5) like obesity, diabetes, hypertension, low HDL and high LDL/Triglycerides. Insulin resistance is the main pathogenic facto behind all these conditions.

Data of Framingham Heart study shows that NAFLD is strongly associated with the MS. Therefore, preventive measures against NAFLD cannot be isolated but holistic measures should be applied against all components of MS. Moreover all components act as risk factors for other components and together they have a synergistic effect on mortality and morbidity.[27]

Drugs- Many drugs are being used for secondary prevention of NAFLD so that development of inflammation and fibrosis can be prevented at the early stage of the disease. Orlistat is a weight reducing medicine which can be an effective treatment of NASH. An initial trial of Metformin showed decreased steatosis and inflammation but no change in fibrosis. Metformin acts in various ways – it decreases hepatic gluconeogenesis, increases hepatic and peripheral insulin sensitivity, slows intestinal glucose absorption and reduces serum lipid level and hepatic fatty acid oxidation.[28] Pioglitazone is also an insulin sensitizer and shows improvement in liver injury and fibrosis in patients of NASH, but weight gain and other side effects limit its utility. Acarbose improves postprandial hyperglycemia by delaying the release of glucose from complex carbohydrate in the absence of an increase of insulin secretion, so it may be a therapeutic strategy to manage NAFLD. Vitamin E is the most promising therapeutic agent at present which has shown its effect on fibrosis also. Vitamin E is an antioxidant which acts by decreasing lipid peroxidation and its antioxidant properties prevent hepatocellular injury. [29] Ursodeoxycholic acid (UDCA) is another important drug which replaces endogenous bile acids (which are hepatotoxins) and also has membrane stabilizing and cytoprotective effect. UDCA protects hepatocytes from injury and decreases oxidative stress in the patient of NAFLD.[30] Omega-3 fatty acids and statins are other drugs which can be used in future. Today these are under trial. In many studies, it was seen that combination therapy of Vitamin C and UDCA significantly improved liver function tests and steatosis of the liver.

Recent Emerging Risk Factors- Besides the above traditional factors some new factors are emerging which are related to our modern lifestyle. Short sleep duration and altered sleep time have a detrimental effect on metabolism and IR. The exact mechanism is not understood but it is seen that there is a U shaped relation between sleep duration and metabolic risk. [31] Depressive illness and treatment of depression are also related to diabetes and insulin resistance. In a modern way of living, people are exposed to many types of environmental toxins due to pollution of air, water, and food. These environmental toxins may accumulate in adipose tissue and act as endocrine disruptors, leading to deregulation of glucose and lipid metabolism. Low birth weight, fetal malnutrition, maternal obesity, and maternal hyperglycemia are also risk factors in the early life which may help in the development of IR and other components of MS in the later life.

CONCLUSION:

The non-alcoholic fatty liver disease has become very prevalent all over the World due to the modern way of living characterized by physical inactivity, obesity, high fat, and sugar consumption, low fiber and low PUFAs in the diet, stress, and strain and exposure to many environmental toxins. The key pathogenic factor in NAFLD is insulin resistance and deregulation of lipid and sugar metabolism. NAFLD is a part of metabolic syndrome, so prevention of NAFLD should be directed against prevention of all components of metabolic syndrome.

Prevention of maternal malnutrition, maternal hyperglycemia and intrauterine fetal malnutrition and prevention of childhood obesity are the initial steps of prevention. Physical exercise and leading a physically active life is the main strategy of prevention. Diet regulation is also equally important. Low sugar especially sucrose, low saturated fat, low-calorie diet, high omega-3 fatty acid containing food and high fiber diet are recommended. DASH (Dietary Approach to Stop Hypertension) food can also be recommended for the prevention of NAFLD. These are the fatless dairy product, fish, germinated cereals, fruits and vegetables, and less salt, fat, and sugar intake. Making the environment safer and pollution free, and life more stress and strain-free is also important.

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