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A Review of Association of Fatty Liver in Non Alcoholics with Metabolic Syndrome Using Fatty Liver Index Supported By Elastography

[1]Vaishnavi Danasekaran and [2*]Lokesh .S,
[1]*Junior resident ,Department of General Medicine,Mahatma Gandhi medical College,Puducherry*
[2*]*Professor and HOD ,Department of General Medicine ,Mahatma Gandhi Medical College,Puducherry*

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ABSTRACT:NAFLD is being considered the hepatic component of metabolic syndrome. It is now the most common cause of chronic liver disease worldwide and needs to be addressed as it is asymptomatic and widely prevalent and can progress to cirrhosis and hepatocellular carcinoma thus necessitating the need for simpler methods to enable detection in modern day practice which will help identifying vulnerable subjects and bring about awareness and lifestyle modifications focused on reversal of the condition. This review of literature was conducted through an internet search on public access websites like Pubmed and Google scholar and concluded that the fatty liver index is a reliable predictor of fatty liver in people with metabolic syndrome .The grade of fatty liver increases with increase in waist circumference .Ultrasound and Elastography are reliable non invasive methods of detecting fatty liver .BMI and Waist circumference are strong predictive factors for fatty liver.

KEYWORDS: Metabolic syndrome/Fatty liver index/NAFLD/Elastography /USG/Correlation

I. INTRODUCTION

Non- alcoholic fatty liver disease is a major cause of chronic liver disease worldwide.(Bedogni et al., 2006) Its prevalence in Indian population ranges from 5 to 28%, which is comparable to the West.(Amarapurkar et al., 2007)

Metabolic syndrome is a cluster of conditions that increase the risk of heart disease, stroke and diabetes .Incidence of fatty liver in people with metabolic syndrome is now very common because of increased urbanization and changing food habits and sedentary lifestyle.(Duvnjak et al., 2007)Obesity and its adverse effects, especially type2diabetes and hypertriglyceridemia, are the main factors responsible for the current epidemic.(Bellentani et al., 2000)

Non-alcoholic fatty liver disease (NAFLD) is now considered the hepatic equivalent of metabolic syndrome.(Bellentani, 2017) Excess fat in the body is stored in our liver cells in >5 to 10% manifests as fatty liver. This condition which is called as Non Alcoholic Steato hepatitis leads to liver inflammation which in turn leads to scarring- irreversible damage –cirrhosis –liver failure

During the last two decades, NAFLD has become the most common chronic liver disease in north America and Europe, but until recently what was thought to be uncommon (perhaps due to the lack of adequate studies in Asia.(Amarapurkar et al., 2007) Fatty liver can be identified on imaging modalities (ultrasonography, computed tomography scans, and magnetic resonance imaging, Elastography and liver biopsy) .(Khov et al., 2014) The fatty liver index calculator takes into account the BMI,Waist circumference,Triglycerides and GGT of an individual and using the algorithm formulated by Bedogni et al detects fatty liver.(Bedogni et al., 2006)

This article attempts to highlight our current knowledge of the prediction of fatty liver in non-alcoholics with metabolic syndrome,using the fatty liver index(FLI).The FLI is correlated with USG and Elastography findings of the liver

II. REVIEW OF LITERATURE

Obesity is a pandemic and brings with it a constellation of problems .Fatty liver due to ethanol is widely studied but Non alcoholic steatohepatitis (NASH) is an emerging entity which emphasizes on fatty liver secondary to increase in BMI, Waist circumference, Triglycerides in an individual.

In studies conducted in Europe and China previously on Fatty liver , BMI and Waist

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circumference were found to be more predictive risk factors than ethanol intake. Based on this Fatty liver index calculator was derived which using four parameters, BMI,Waist circumference, Triglycerides and GGT calculating the FLI between 0 to 100 , if <30 ruled out fatty liver 30-60 posed an intermediate risk of fatty liver and >60 suggests fatty liver (Bedogni et al., 2006) .Non alcoholic fatty liver disease (NAFLD) is the most common liver disease and estimated to be 20-30% in general population of Western countries (Bedogni et al., 2005). It occurs as a histologically classified as simple steatosis and nonalcoholic steatohepatitis(NASH). It was believed to be a benign condition but is now being recognized as a major cause of morbidity and mortality concerning the liver (Paschos and Paletas, 2009)

NAFLD may progress to cirrhosis, liver failure, and hepatocellular carcinoma.NAFLD is strongly associated to metabolic syndrome . Insulin resistance plays a major role in both NAFLD and metabolic syndrome. So much that it in now believed that fatty liver is the hepatic manifestation of metabolic syndrome (Gastaldelli, 2010) . Excessive hepatocyte triglyceride accumulation resulting from insulin resistance is the first hit in the proposed 'two hit' model of the pathogenesis of NAFLD. Oxidative stress resulting from mitochondrial fatty acids oxidation, NF-kappaB dependent inflammatory cytokine expression and adipocytokines are all considered to be the potential factors causing second hit which lead to hepatocyte injury,inflammation and fibrosis(Duvnjak et al., 2007). Alterations in lipid metabolism associated with insulin resistance result from the interaction between the effects of insulin resistance located primarily in muscles and adipose tissue and impact of the compensatory hyperinsulinemia on tissues that remain insulin sensitive. These alterations include enhanced peripheral lipolysis, increased hepatic uptake of FFAs and increased hepatic triglyceride synthesis. FFA influx and neosynthesis outweigh FFA oxidation and triglyceride secretion, resulting in the net effect of hepatic fat accumulation. This can explain a key role of insulin resistance in the development of hepatic steatotosis(Duvnjak et al., 2007) .Fatty liver usually does not have specific symptoms, at the early stages, which limits early identification. Liver biopsy is the gold standard for quantifying liver steatosis in fatty liver disease (Yang et al., 2015). However, it is not regularly done because is an invasive procedure .Hence, the diagnosis of fatty liver is usually made by ultrasonography and elastography .

Non-alcoholic fatty liver disease prevalence in Indian population ranges from 5 to 28%, which is comparable to the West(Amarapurkar et al., 2007). Obesity is not only a risk factor for NAFLD but also determine severity of NAFLD Also, the Asians are known to develop central obesity at lower BMI (Amarapurkar et al., 2007). The spectrum of NAFLD ranges from simple steatosis, non-alcoholic steatohepatitis to cirrhosis[1].In a recent population-based epidemiological study , Asians had 2- to 3-fold increase in insulin resistance and 2-fold increase in hepatic triglyceride content(Amarapurkar et al., 2007). Recent concepts also suggest that the magnitude of adipose tissue dysfunction may have more metabolic impact than the severity of adiposity[1]. Also, lower preponderance of adiposity in Indian NAFLD is well-documented however, data on clinical characteristics, metabolic profiles, and histopathological severity in patients with lean NAFLD in comparison to the overweight or obese NAFLD patients is scant (Amarapurkar et al., 2007)

A case-control study, in Italy found that body mass index (BMI) was a stronger risk factor for FL compared to ethanol intake in the population of north Italy(Bedogni et al., 2005). Interestingly, this finding was confirmed by a study performed in China(Yang et al., 2015).Waist circumference has long been hypothesized to be a predictor of FL independently from BMI, but data for the general population were not available until very recently(Bedogni et al., 2005) .Because BMI is a surrogate index of body adiposity , direct indexes of adiposity such as skin folds can be of value when studying the relationship between body fat per se and disease (Amarapurkar et al., 2007). Hyperinsulinemia and insulin resistance are common in subjects with FL independently from BMI and thus are expected to be markers of FL in the general population . Inspite of the operational separation of FL into alcoholic and non-alcoholic fatty liver disease (NAFLD) , the relative contribution of ethanol intake and other factors in the pathogenesis of FL is still uncertain. An algorithm was developed for the prediction of FL in the general

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population (Bedogni et al., 2006).
FLI is thus calculated as:
FLI = (e0.953*loge (triglycerides) + 0.139*BMI + 0.718*loge (ggt) +0.053*waist circumference - 15.745) / (1 + e
0.953*loge (triglycerides) +0.139*BMI + 0.718*loge (ggt) + 0.053*waist circumference - 15.745) * 100 (1)
It can be applied as follows,
If a patient has a BMI : 31kg/m2, Waist circumference: 102cm , TGL:155 and, GGT:20 ,the above mentioned algorithm can be used in Fatty liver index- MD Calc and in this patient
FLI: 72 (HIGH RISK)
This patient has a definite possibility of fatty liver which can be confirmed radiologically with Ultrasound and Elastography.

Another study aimed to evaluate the accuracy and optimal cut-off point of the FLI for predicting non-alcoholic fatty liver disease (NAFLD) in China using Ultrasound evidence for confirmation was done and had similar results. Anthropometric and biochemical features were collected by a standard protocol. NAFLD was diagnosed by hepatic ultrasonography. The accuracy and cut-off point of the FLI to detect NAFLD were evaluated .The prevalence of non-alcoholic fatty liver disease in overweight and obese patients with Type 2 diabetes is high(Dasarathy et al., 2009).Multiple metabolic disorders were significantly associated with non-alcoholic fatty liver disease in overweight and obese patients with Type 2 diabetes. In non-alcoholic fatty liver disease (NAFLD), real time ultrasound has high specificity in identifying hepatic steatosis(Dasarathy et al., 2009)

METABOLIC SYNDROME AND ITS RELATIONSHIP WITH FATTY LIVER

According to National Cholesterol Education programme (NCEP) Adult treatment panel III criteria in 2001(modifications for use in Asian population by Heng D et al) (Heng et al., 2006) a person should have atleast three of the following five criteria to be classified as a case of metabolic syndrome.It was later modified in 2005 by the American Heart Association (AHA) and National Heart Lung and Blood Institute with a few modifications as follows (Paschos and Paletas, 2009)
Waist circumference of >102 cm for males and >88cm for females
Known hypertensive on medication or BP > 130/80mmHg
Known diabetic on medication or fasting blood sugar >100 -125mg/dl
Hypertriglyceridemia on medications or serum triglyceride >150mg/dl
Low HDL cholesterol levels <50mg/dl for women and <40mg/dl for men or on medications for dyslipidemia
Were labelled to have metabolic syndrome(Paschos and Paletas, 2009), (Kumar et al., 2013)

Insulin resistance was found to be the common pathophysiological mechanism in both NAFLD and Metabolic syndrome.Recent literature emphasizes that insulin resistance ,oxidative stress induced lipid peroxidation ,adipokines, pro inflammatory cytokines and mitochondrial dysfunction leads to the development and progression of Fatty liver.

Tsuneto et al discovered that age,increased BMI,increased levels of triglycerides and being hypertensive had an influence on a person developing faty liver disease.
There seems to be a strong predictive factor for persons with high BMI and visceral fat to have hepatic steatosis(Gastaldelli, 2010)

Increased triglycerides , independent of obesity seems to influence the onset of fatty liver and patients with diabetes have more visceral and intrahepatic fat compared to non-diabetics of similar BMI.(Gastaldelli, 2010) Intrahepatic steatosis is highly correlated independent of obesity to all the individual components of metabolic syndrome.(Gastaldelli, 2010)

Tsuneto et al in their study declare that people who developed fatty liver had high BP,high TGL,low HDL,and increased BMI through their study period .(Gastaldelli, 2010)

NAFLD is both the cause and consequence of Metabolic syndrome with a high prevalence especially in the cohort of people who share metabolic co-morbidities like diabetes and hypertension .(Pardhe et al., 2018)
Early diagnosis is crucial in the management of NAFLD and there is no one single biochemical marker which is elevated that points towards the confirmation of fatty liver .Hence various risk factors which forms a component of metabolic syndrome along with blood parameters in combination give a more reliable prediction(Pardhe et al., 2018)

OBESITY AND FATTY LIVER ASSOCIATION

Obesity has been described to be the primary component leading to metabolic syndrome .In muscle cells and fat cells of obese individuals ,binding of insulin to its receptor,its phosphorylation ,activity of tyrosine kinase etc are reduced.High adipose energy storage in obese

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individuals leads to an increased free fatty acid influx and increased TGL storage which leads to insulin resistance and other adverse effects(Paschos and Paletas, 2009).(Kahn and Flier, 2000)

As the amount of visceral fat increases it secretes adipocytikines like TNF and IL-6 which results in the patient developing hypertension .These individuals also have high sodium and water reabsorption at proximal tubules(Paschos and Paletas, 2009), (Katagiri et al., 2007)

In diabetes and obesity the main cause of insulin resistance is that there is downregulation of GLUT 4 in the adipocytes .In skeletal muscle of the same individuals GLUT4 expression is normal but there appears to be a defective glucose transport due to ineffective translocation and fusion of vesicles containing GLUT4 to the plasma membrane(Kahn and Flier, 2000)

Hence the condition of obesity where the predominant cells are adipocytes suggests that the function of adipocytes is increased where it acts as an endocrine gland with multiple effects on several organs including the brain and liver releasing hormones such as leptin and cytokines like TNF alpha and FFA's and holds a pivotal role in glucose homeostasis and energy balance (Kahn and Flier, 2000)

WAIST CIRCUMFERENCE AND INSULIN RESISTANCE IN FATTY LIVER

Recent research suggests that the intra abdominal adipocytes due to their adrenergic receptors are lipolytically more active ,thereby increasing FFA influx,which inhibits insulin clearance and promotes insulin resistance by uncertain mechanisms(Kahn and Flier, 2000).Hyperinsulinemia as such can lead to insulin resistance by insulin receptor downregulation and postreceptor pathway desensitization(Kahn and Flier, 2000).This results in reduced insulin receptor expression,hyperlipidemia and glucose intolerance without any genetic defect in insulin secretion or action.Intra abdominal adipocytes have a stronger relationship with insulin resistance ,cardiovascular disease and diabetes than the peripheral subcutaneous or gluteal fat deposits(Kahn and Flier, 2000).

HYPERTENSION AND FATTY LIVER ASSOCIATION

Hypertension and NAFLD are linked in ways such that hypertension is a component of Metabolic syndrome that develops as a result of insulin resistance leading to NAFLD and NAFLD due to complex interactions explained below leads to the onset of hypertension in a previously normotensive individual .Increased activation of the sympathetic nervous system,enhanced sodium reabsorption in the kidneys secondary to hyperinsulinemia and impaired vasodilation due to stimulation of insulin.Several studies have shown that NAFLD posed an increased risk of hypertension in the next few years to follow in that individual(Kim et al., 2018)

In a study by Oikonomou et al (Oikonomou et al., 2018)it was concluded that NAFLD is associated with new onset HTN and increased blood pressure is related to onset of fatty liver disease and further progression to liver fibrosis.

Insulin resistance and RAAS activation provides potential pathophysiologic links between the two entities(Oikonomou et al., 2018) .Hence ,patients with HTN should be thoroughly evaluated for NAFLD and vice versa and advised lifestyle and treatment modifications accordingly.There is evidence of RAAS inhibitors decreasing isulin resistance and progression of fibrosis in NAFLD(Oikonomou et al., 2018)

DYSLIPIDEMIA AND FATTY LIVER ASSOCIATION

Dyslipidemia - increased triglycerides (hypertriglyceridemia) and low HDL-C(High density lipoprotein) have been observed to be associated with NAFLD.The secretion of fatty acids and VLDL into the plasma is high in persons with NAFLD or Metabolic syndrome compared with others (Kim et al., 2018).There is an increased contribution from non systemic fatty acids which are primarily derived from lipolysis of intrahepatic and visceral fat and also by de novo lipogenesis(Kim et al., 2018).In a normal scenario insulin reduces VLDL production by reducing or suppressing adipose tissue lipolysis and production of VLDL from liver.In a person with Metabolic syndrome or NAFLD this fails to occur causing a raised triglyceride and low HDL-C concentration(Kim et al., 2018).

In a recent study by Kim et al in 2018(Kim et al., 2018) it was found that 23 percent patients with NAFLD had isolated high TGL ,10% had isolated low HDL-C and 18% had dyslipidemia (both high TGL and low HDL-C).

OTHER INDEXES OR ALGORITHMS USED TO PREDICT FATTY LIVER

There have been other methods of calculating or predicting fatty liver

These algorithms are used variables as mentioned below.One of the early scoring systems that was developed was BAAT score which combined 4 clinical variables ie:

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BMI>28kg/m2,Age >30 years,ALT>2Xnormal and serum TGL >150mg/dl.It showed a good PPV in detecting advanced fibrosis but fell short of identifying mild to moderate disease.

Fibro test was another algorithm which used 5 biochemical markers which included ApolipoproteinA1,Total bilirubin,GGT, Haptoglobulin and 2-macroglobulin.It was a simple, quantitative and non-invasive estimate of liver fibrosis ,but had the same drawbacks of the BAAT scoring system where advanced fibrosis was easily detected but mild and moderate stage could not be assessed .

NAFLD fibrosis scoring system used 6 commomly calculated parameters which included BMI, Age, Hyperglycemia, Albumin level ,AST/ALT ratio and platelet count.It could predict presence or absence of fibrosis in nearly 90% of the sudy populace.

The Original European Liver Fibrosis (OELF) test used Age,,Tissue inhibitor of Matrix Metalloproteinase (TIMP 1),N-t propetide of type III collagen(P3NP) ,Hyaluronic acid.This method had a sensitivity of 92 % but cannot be practiced in all centres all over the world particularly in developing countries which form a major burden of NAFLD .

USE OF ULTRASOUND IN THE PREDICTON OF FATTY LIVER

Ultrasonography is a noninvasive ,low cost,easily available and reliable tool in the diagnosis of fatty liver. Clinical evidence using the fatty liver index gives us an idea about identifying patients who have to undergo ultrasonography and will most probably have a fatty liver , thereby reducing the need for liver biopsy which is an invasive and painful procedure for the patient(Khov et al., 2014)

Bright hepatic echoes,vascular blurring of hepatic or portal vein and increase in the hepatorenal echogenicity are some of the classical features of NAFLD in ultrasound.(Khov et al., 2014)

Also when compared with people who had non-NAFLD related liver diseases had a thicker subcutaneous tissue .NAFLD was rarely seen in patients with subcutaneous tissue less than 20 mm(Khov et al., 2014)

Features suggestive of fatty liver on ultrasound were arrived upon as

Liver was found to be uniformly heterogenous .Subcutaneous tissue depth was >2cm.(around the waist).Entire field was filled by the liver with no visible edges .Image quickly attenuated at 4 to 5 cm of depth making it difficult to see underlying deeper structures. Brightness within first 2 to 3 cm of depth(Khov et al., 2014). In a study done by Riley et al it was demonstrated that clinicians can be trained in identifying ultrasound images diagnosing NAFLD after a short 20 minute training session.

According to the American Gastroenterology Association fatty liver in USG is graded as the following ,

Grade 1: increased hepatic echogenicity along with visible periportal and diaphragmatic echogenicities.

Grade 2 : Increased hepatic echogenicity alon with imperceptible periportal echogenicity,with no obstruction of the diaphragm.

Grade 3 : Increased hepatic echogenicity along with imperceptible periportal echogenicity and obstruction of the diaphragm.(Singh et al., 2017)

In a study by Dasarathy et al (Dasarathy et al., 2009),patients mostly females having a BMI>30,Age >55,TGL>250 along with diabetes had significant correlation in ultrasound a liver biopsy ,proving NAFLD

Hence identifying appropriate clinical risk factors supported by consistent ultrasound findings can lead to the correct diagnosis of NAFLD thereby preventing the need for invasive testing in early stages .(Khov et al., 2014)

Another study done by Lee et al(Lee et al., 2010) derived upon the conclusion supported by liver biopsy that there was a sensitivity of 92% of having a fatty liver in ultrasound when hepatic steatosis was more than 30%.

However there are a few fallbacks when diagnosing fatty liver using ultrasound as it cannot be used to correlate the degree of fibrosis.Reliability is poor in severe obesity as liver echogenicity will be altered when there is plenty of subcutaneous fat.Similarly it is of little use in patients with pre-existing liver disease eg:chronic hepatitis C and inability to detect when hepatic steatosis is less the 20%.(Khov et al., 2014)

ELASTOGRAPHY IN FATTY LIVER PREDICTION

There are 2 different approaches for measuring liver stiffness:

1 . Ultrasound-based shear wave elastography

2. Magnetic resonance–based elastography

In the first method ultrasound is used to detect the velocity of microdisplacement (shear waves) induced in liver tissue, whereas the second method uses magnetic resonance scanner(Castera et al., 2019). The shear wave's velocity is converted into a liver stiffness measurement (LSM), which is expressed in kilopascals (kPa) or meters per second. Vibration-controlled transient

elastography has been the most used ultrasound-based technique worldwide, but newer modalities like point shear wave elastography (pSWE), are emerging(Castera et al., 2019).

Shear Wave Elastography reported diagnostic accuracies of 91% and 95% for advanced fibrosis and cirrhosis, and optimal cutoffs of 9.2, and 13.5 kPa, respectively. SWE in comparison to transient elastography in NAFLD patients was significantly better for predicting advanced fibrosis The sensitivity >90% for cutoff values of 8.3 kPa and 10.5 kPa for advanced fibrosis and cirrhosis(Castera et al., 2019)

Point shear wave elastography (pSWE) , an acoustic radiation force impulse (ARFI)-based method is a recent non-invasive tool for grading liver fibrosis . ARFI makes use of a short duration high intensity acoustic pulse to move tissue perpendicular to the tissue surface (Leong et al., 2019). The transducer then identifies tissue displacement in a focused spot along the radiation force and tissue stiffness is obtained . In pSWE, shear waves which are perpendicular to the longitudinal waves are calculated . Additional equipment is not needed for shear wave elastography as it can be incorporated into a USG with B-mode(Khov et al., 2014). Direct visualization of anatomy allows the operator to select a particular area, avoid large vessels or the biliary system (Leong et al., 2019)

III. CONCLUSIONS

BMI and Waist circumference are strong predictive factors for fatty liver. Diabetes, Dyslipidemia and Hypertension as components of metabolic syndrome are strong predictive factors of fatty liver .The fatty liver index is a reliable predictor of fatty liver in people with metabolic syndrome even without the aid of radiological investigations. The grade of fatty liver increases with increase in waist circumference and BMI**.**Ultrasound and Elastography are reliable non invasive methods of detecting
fatty liver .

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