Review Article

Lean Non-Alcoholic Fatty Liver Disease (NAFLD)

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ARTICLE INFO

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[https://doi.org/https://doi.org/
10.2776/ub.crjim.2020.001.01.6](https://doi.org/https://doi.org/10.2776/ub.crjim.2020.001.01.6)Received on March 20th, 2020;Revised on March 24th, 2020;Accepted on Apr 5th, 2020

ABSTRACT

Non-Alcoholic Fatty Liver Disease (NAFLD) is a condition that can develop into advanced liver disease. The NAFLD spectrum includes simple steatosis, non-alcoholic steatohepatitis (NASH), liver fibrosis, and liver cirrhosis to hepatocellular carcinoma. One of the underlying pathophysiologies is insulin resistance found in metabolic syndrome. People with metabolic syndrome are not always obese, and NAFLD can also be found in this group, known as lean NAFLD, which has different metabolic characteristics. Metabolic characteristics of lean NAFLD include high levels of transaminases and insulin, low insulin sensitivity, low fasting glucose, low necroinflammatory activity, and liver fibrosis. Some related factors are methionine and choline deficiency, excessive acyl-coA expression, and PNPLA3 gene polymorphism. Lean NAFLD is an interesting topic to discuss because practitioners' awareness of lean NAFLD is lower compared to obese patients. NAFLD is a risk factor for chronic diseases such as cardiovascular disease, kidney disease, colorectal, atrial fibrillation, and hypothyroidism, so it is essential to be recognized by clinicians. To date, there are no guidelines or recommendations that discuss specific treatments in this lean NAFLD population.

Keywords: NAFLD, lean NLFD

INTRODUCTION

Non-Alcoholic Fatty Liver Disease (NAFLD) is a condition that is increasingly being realized can develop into advanced liver disease. The NAFLD spectrum includes simple steatosis, non-alcoholic steatohepatitis (non-alcoholic steatohepatitis / NASH), liver fibrosis, liver cirrhosis, and hepatocellular carcinoma.^[1] Patients with NAFLD are caused or associated with one or more components of metabolic syndrome, which is insulin resistance, impaired glucose and diabetes mellitus.^[2] NAFLD has been known to be tolerance with obesity, but NAFLD can also be found in patients with normal BMI without insulin resistance or diabetes mellitus, which is referred to as "lean NAFLD". Lean NAFLD is known to have metabolic characteristics that are different from NAFLD-obesity. Metabolic characteristics of lean NAFLD include high levels of transaminases and insulin, low insulin sensitivity, low fasting glucose, and low necro-inflammatory activity and liver fibrosis.^[3]

Margariti *et al.* in the Annals of Gastroenterology emphasize the fact that the majority of NAFLD patients in tertiary care have a normal BMI (lean).^[4] Kim *et al.* show that the prevalence of lean NAFLD in Western populations is around 16%. It is almost the same as in Asian populations that around 15% to 21%.^[5,6] It shows that Asians have the same risk of developing NAFLD as Westerners, even with different clinical characteristics. Lean NAFLD is an interesting topic to discuss because NAFLD is a risk factor for chronic diseases such as cardiovascular, kidney, colorectal cancer, atrial fibrillation and hypothyroidism.^[7] Also, the lack of vigilance of clinicians in diagnosing lean NAFLD results in late intervention to patients. Recent research raises several important issues related to lean NAFLD, is lean NAFLD only a disease that is at risk of becoming a more severe disease or just the same disease with the metabolic profile of NAFLD without weight gain?

Definition

The AASLD Practice Guideline (2012) defines fatty liver as a condition due to excessive fat accumulation in the form of triglycerides (steatosis) in the liver (histologically > 5% of hepatocytes).^[8] Based on the Chinese National Workshop on Fatty Liver Disease in 2010, the diagnosis of NAFLD is based on criteria:^[9]

- (1) Alcohol consumption <140 grams/week in adult men and <70 grams/week in adult women
- (2) Do not suffer from hepatitis B or C, hepatolenticular degeneration, autoimmune diseases, history of total parenteral nutrition or consumption of hepatotoxic

drugs (such as tamoxifen, amiodarone, sodium valproate, methotrexate, and glucocorticoid); and (3) Ultrasound examination shows fatty infiltration in the liver.

Based on the 2016 EASL guidelines, the diagnosis of NAFLD requires the exclusion of alcohol consumption gram 30 grams in men and ≥ 20 grams in women. NAFLD is closely related to obesity, insulin resistance, and glucose intolerance, but NAFLD can occur in patients with normal BMI without any other metabolic risk known as "lean NAFLD". Until now, there are still differences in the setting of normal BMI standards. In Western studies using BMI $<25 \text{ kg} / \text{m}^2$ as a NAFLD lean cut-off while some studies in the Asia Pacific use a BMI $<23 \text{ kg} / \text{m}^2$ as a NAFLD lean cut-off.^[10]

Prevalence

The prevalence of NAFLD throughout the world is increasing, in line with the increasing prevalence of obesity, hyperlipidaemia and diabetes mellitus in the general population. In Indonesia, research on NAFLD is very limited. Lesmana reported 17 patients with non-alcoholic steatohepatitis (NASH) have an average age of 42 years, with 29% of the histology of the liver showing steatohepatitis accompanied by fibrosis. A study with a large sample by Hasan *et al.* found a prevalence of

non-alcoholic fatty liver (NAFLD) of 30.6%. Important risk factors that are reported are obesity, diabetes mellitus, and hypertriglyceridemia.^[11] At RSUP dr. Kariadi Semarang using liver ultrasound examination in 2005-2009 found an increase in cases of fatty liver from year to year, each year is 4%, 4.5%, 5%, 6% and 7%.^[12]

Margariti *et al.* in the Annals of Gastroenterology emphasize the fact that the majority of NAFLD patients in tertiary care have a normal BMI. The study examined 162 patients with hepatic steatosis and found that every 1 of 8 NAFLD patients had a normal BMI. It is consistent with the results of studies in India about rural populations with a low prevalence of NAFLD, 75% of NAFLD patients have a BMI below 25kg / m² and 54% without overweight or abdominal obesity.^[4] The prevalence of lean NAFLD in the United States is 7%, in Japan 15.2 %, in Korea 12.6%, in Taiwan 4.2%, and in Zhejiang 7.2%. The majority of lean NAFLD are workers and under 45 years old. It shows the possibility of insulin resistance causes an increase in fat accumulation in the population of Southeast Asia compared to Western populations even though BMI is within normal limits.^[13]

Pathogenesis

NAFLD is a cause of chronic liver disease and is an indicator of metabolic syndrome, which is currently increasing in prevalence. NASH is one of the heavier NAFLD spectra defined as the presence of steatosis with progressive inflammation and fibrosis. However, the pathogenesis of NAFLD to NASH is not yet fully known. Conditions that are often associated with NASH are obesity, diabetes mellitus, and insulin resistance. The hypothesis which has so far been widely accepted is "the two-hit theory" proposed by Day and James.^[14]

Figure 1. The theory of "multiple parallel hits" ^[15]

Research by the Genome-wide association study (GWAS) states the importance of the polymorphism of the patatin-like phospholipase 3 gene (PNPLA3) in NAFLD. Genetic polymorphisms can distinguish simple fatty with or without minimal inflammation and progression of fibrosis to NASH. In some cases, inflammation can precede steatosis and anti-tumor necrosis factor (TNF) - α antibodies improve steatosis in ob/ob mice. Obesity and diabetes induce insulin resistance, adipocyte proliferation and changes in the intestinal flora. Adipokines such as IL-6 and TNF- α produced by adipocytes affect the fat component of hepatocytes and cause inflammation in the liver. Signals from Gut can be influenced by the consumption of trans fatty acids, fructose or TLR ligands. Use of free fatty acids and free cholesterol induces ER stress and oxidative stress which causes inflammation and fibrogenesis.^[15]

What is the pathogenesis of "lean NAFLD"?

Several studies have been conducted to determine the pathogenesis of fatty liver in populations with normal BMI. One of the studies with experimental animals is mice with a deficiency of methionine and choline deficiency. The treatments above cause mice to experience neither insulin resistance nor

obesity but a decrease in body weight and fat accumulation in the liver. It is a consequence of decreased beta-oxidation of fatty acids and decreased very low-density lipoproteins (VLDL), so triglycerides are

removed from cells.^[16-17]

In studies of mice with genetic modification, they produce an overexpression of acyl-CoA: diacylglycerol acyltransferase 2 (DGAT2), which functions as a catalyst in the final step of triacylglycerol biosynthesis. In these mice, hepatic steatosis occurs with increased triglycerides, diacylglycerol, ceramides, and unsaturated long-chain fatty acyl-CoAs, without insulin resistance or impaired glucose metabolism.

In humans, genetic polymorphisms are known to be associated with the incidence of hepatic steatosis without obesity or insulin resistance. One genetic study that is often investigated is the polymorphism of the PNPLA3 gene. Other studies show that polymorphisms in the I148M gene are associated with lipolytic activity and increased levels of aminotransferase without insulin resistance.^[19]

The Role of PNPLA3 I148M mutation in fatty liver disease

Although it has been proven that PNPLA3 has hydrolase activity, the physiological role *in vivo* is still unclear. Whether the excessive expression of PNPLA3 in cell 293 HEK or the destruction of murine 3T3-L1 adipocytes affects cellular triglyceride levels. To better explain the role of PNPLA3 in fatty liver disease, He et al. have just explained the effect of I148M substitution on localization and *in vitro* activity. Subcellular fractionation experiments explain that wild-type PNPLA3 is closely related to lipid membrane fraction and lipid droplet localization in Huh-7-line human hepatoma cells after oleate administration. Although there is no evidence of the mislocalization of the 148M PNPLA3 mutant, triglyceride lipase activity disappears, causing triglyceride accumulation in Huh-7 cells, which manifests as greater and greater fat droplets. Furthermore, acute overexpression of mutant protein in mice causes a doubling of the level of fat in the liver. However, overexpression of wild-type protein fails to reduce liver fat levels

in vivo. In line with findings from population studies, expression of the mutant protein was not related to differences in levels of free fatty acids, phospholipids or free cholesterol in rats.^[19]

Besides, to work as a lipase, PNPLA3 have acylglycerols transacetylase activity, including the conversion of fatty acids to monoacylglycerol and diacylglycerol. However, it has not been proven yet *in vitro*. The actual role of PNPLA3 may differ from tissue to tissue, and it remains unclear whether the main effect on the liver is to hydrolyse triglycerides or transfer of fatty acids.^[19]

In addition to gene polymorphisms, the research of Visser ME et al. Shows that the condition of hypobetalipoproteinemia is associated with severe NAFLD events without being accompanied by an increased metabolic risk.^[20]

Role of Insulin Resistance in lean NAFLD

The cause of NAFLD in patients with normal BMI and without metabolic risk factors is not yet fully known. The underlying pathogenesis is multi-factorial in which genetic and dietary factors are associated with the development of lean NAFLD even without metabolic abnormalities. Research in Japan shows that diets high in cholesterol and low in polyunsaturated fatty acids are higher in lean NAFLD patients than controls, and high consumption of canned drinks and meat is associated with an increased risk of NAFLD, independent of BMI.^[4]

Regardless of dietary habits, NAFLD was found to be associated with insulin resistance, independent of BMI. The lack of evaluation of serum insulin levels and insulin resistance is a drawback in this study. Still, other studies have shown that insulin resistance is found in lean NAFLD even without other metabolic syndromes. Since it is known that insulin resistance levels and the prevalence of metabolic syndrome have increased from lean to overweight or obese, this has led to the assumption that NAFLD is the first consequence

of insulin resistance before progressing to clinical metabolic abnormalities.^[4]

Although NAFLD has a strong relationship with insulin resistance, this is not found in all cases. Review of Tilg and Moschen mentions that inflammation is the beginning of hepatic steatosis. In the review, the authors mention that steatosis is a "bystander phenomenon" and not a cause of inflammation, adopting the multiple hits hypothesis in explaining the pathogenesis of NAFLD. It is in line with Sanyal's research which showed a significant improvement in the liver histology of NAFLD patients who were given Vitamin E (antioxidant agent), without changing the level of insulin resistance. These data open up knowledge of the mechanisms associated with the development of hepatic and inflammatory steatosis, which may be applicable to lean NAFLD.^[4]

Hyperinsulinaemic-euglycaemic clamp studies show that an increased of intrahepatic triacylglycerol (IHTG) is strongly associated with insulin resistance in the liver, skeletal muscle and a large percentage of liver fat. Thus,

even though the amount of IHTG is slightly associated with metabolic dysfunction. Besides, animal studies have shown the accumulation of liver fat associated with insulin signalling in the liver through activation of the $\text{C}\epsilon$ protein kinase. This mechanism shows a direct relationship between liver fat and insulin resistance.

Recent studies in patients with FHBL (Familial Hipo Beta Lipoproteinemia), regardless of moderate or severe hepatic steatosis, do not show a decrease in hepatic or peripheral sensitivity to insulin compared with controls. It indicates that the accumulation of triacylglycerol in the liver does not show an association with insulin resistance in the liver or peripherally.

In basal conditions, HOMA-IR tends to be higher in FHBL patients compared to controls. It is due to the high level of basal insulin in patients compared to controls and is

most likely due to a decrease in insulin clearance and is not caused by an increase in insulin secretion. It is in line with previous studies in normal BMI patients, where liver fat accumulation is associated with failure of insulin clearance, independent of obesity.^[20]

Insulin resistance in the liver can also not occur in FHBL despite severe steatosis. The absence of insulin resistance has been previously studied in experimental animals with hepatic steatosis. In this animal, diacylglycerol acetyltransferase (which is the final step catalytic enzyme of triacylglycerol synthesis) is excessive in the liver. Then, deletions of long-chain fatty acid elongase family member 6 (ELOVL6) (which is a microsomal enzyme involved in elongation of fatty acids), deletion of transfer proteins triacylglycerol (responsible for adding triacylglycerol-rich lipoproteins and inhibiting hepatic fatty acid oxidation). All of which are associated with induction of hepatic steatosis with or without hepatic and hepatic resistance.^[20]

In the study of Visser ME *et al.*, hepatic steatosis in FHBL may be the result of the accumulation of harmless triacylglycerols, where NAFLD is the accumulation of toxic lipid metabolites that cause insulin resistance. In this study, NEFA concentrations in circulation did not differ between FHBL and controls. Moreover, the relationship between hepatic steatosis and insulin resistance may be related to genetics. Such APOC3 polymorphisms are known to be associated with NAFLD and insulin resistance, whereas a single nucleotide polymorphism of rs738409 in PNPLA3 is associated with an increase in liver fat without insulin resistance.

However, recent research not adequately addresses the mechanism of the relationship between hepatic steatosis and insulin resistance completely. Hepatic steatosis is possible as a result of insulin resistance in the liver and peripheral. This study shows a unique model of severe fatty liver disease that is not associated

with hepatic or peripheral insulin resistance. Although this study is unable to explain the exact mechanism underlying the complex relationship between hepatic steatosis and insulin resistance, further research is needed that focuses on cohort hepatic steatosis.

Factors related to LEAN NAFLD

Margariti *et al.* in the Annals of Gastroenterology emphasize the fact that the majority of NAFLD patients in tertiary care have a normal (lean) BMI. The study examined 162 patients with hepatic steatosis and found that every 1 in 8 NAFLD patients had a normal BMI. One explanation for the presence of ectopic fat in the liver in subjects with normal BMI can be analogous to the metabolic system of obese patients but occurs in subjects with normal BMI, which occurs in 5% of the western population.^[4]

Research in the Japanese population shows that weight gain in adulthood is a strong predictor of the NAFLD in men.^[13] A 10 kg increase in body weight since age 20 is significantly associated with fatty liver regardless of sex.^[21] Pelvic circumference is independently and significantly related to NAFLD in non-obese (Male: OR 1.11, Female: OR 1.05). Body fat percentage was independently and significantly related to NAFLD in non-obese (Male: OR 1.13). Pelvic circumference and body fat percentage are predictors of NAFLD in the Japanese population.^[13]

In the Chinese population, lean NAFLD has different metabolic characteristics than overweight-obese patients. The NAFLD lean group had lower blood glucose, blood pressure, cholesterol levels, insulin resistance, and lower haemoglobin than the overweight-obese group. Subjects with normal BMI tend to suffer from diabetes, hypertension and metabolic syndrome when accompanied by NAFLD.^[7] Thus, lean NAFLD is a more dangerous condition than NAFLD with overweight-obesity.

Previous studies mention lean NAFLD

patients have greater visceral adipose tissue than overweight and obese patients. The research of Bhat G *et al.* also found that an increase in insulin resistance was proportionally associated with an increase in waist circumference (central obesity), this indicates that central obesity was more related to insulin resistance than BMI. Lean NAFLD may be an initial phase of metabolic syndrome, and increased waist circumference and BMI are the result of an increase in obesity and are a complication in patients in this study.^[22]

Margariti *et al.* showed that increased waist circumference in 1/3 lean NAFLD, metabolic syndrome in 1/5 lean NAFLD and more than 1/2 lean NAFLD met one of the metabolic syndrome criteria.^[4] It is questionable whether patients with lean NAFLD have metabolic syndrome subclinical with ectopic fat as the first manifestation. It is interesting to be evaluated further, especially how the risk of metabolic disorders, insulin resistance or diabetes, cardiovascular events and progression to advanced liver disease in patients with lean NAFLD.

The study of Margariti *et al.* also has some limitations, the diagnosis of NAFLD is not carried out uniformly to all patients, some are diagnosed by ultrasonography and some by liver biopsy which is a standard.^[4] Ultrasonography is accurate in moderate to severe steatosis with a sensitivity of 85% and specificity of 94%.^[23] It allows milder hepatic steatosis in lean patients compared to obesity, which has been established in obese patients with positive ultrasonography that is enough to make the diagnosis and in lean patients the limits for liver biopsy can be lower.

The WHO expert consultation said that most Asians have a higher percentage of body fat compared to whites regardless of age, sex, and BMI. Asians with risk factors for type 2 diabetes and cardiovascular disease show a large proportion even though WHO uses BMI with a cut-off below 25 kg / m².^[24]

Feng *et al.* reported that subjects with

normal BMI tended to suffer from diabetes, hypertension and metabolic syndrome if they had NAFLD, this suggests that normal BMI subjects with NAFLD should be monitored more closely than overweight-obese subjects with NAFLD.^[7]

Management of NAFLD

The management of patients with NAFLD consists of therapy for liver disease as well as accompanying metabolic syndromes such as hyperlipidemia, obesity, insulin resistance, and diabetes mellitus. Based on the 2012 AASLD Practice Guideline, the modalities of NAFLD therapy include:^[8]

1. Lifestyle modification: general weight loss can reduce hepatic steatosis that can be achieved with a hypocaloric diet and/or a combination with physical activity. The recommended exercise program is 2-3x / week for 30-60 minutes over a 6-12-week period. A weight loss of 3-5% can improve steatosis, but a reduction of up to 10% may be needed to improve necroinflammation.
2. Insulin sensitizing agents: metformin has been shown to have no significant effect on liver histology and is not recommended as a specific therapy for NASH. Pioglitazone can be used in patients with liver biopsy showing NASH. However, the safety and efficacy of pioglitazone in the long term has never been studied.
3. Antioxidants: Vitamin E at a dose of 800IU / day can improve liver histology in non-diabetic patients with liver biopsy showing NASH.
4. UDCA is not recommended for NAFLD or NASH.
5. Statins are not recommended as a specific treatment for NASH, but statins are used as a therapy for dyslipidemia in patients with NAFLD or NASH.
6. Foregut bariatric surgery is not contraindicated in obese patients with NAFLD or NASH.

Management of lean NAFLD

Until now, there has been no recommendation of appropriate therapy for patients with lean NAFLD, whether diet and exercise are still useful in NAFLD patients with a normal BMI are still in further research. Recent research has found that new lifestyle

changes can prevent the development of type 2 diabetes. As is known, type 2 diabetes is an important consequence of severe insulin resistance, and NAFLD is an initial consequence of insulin resistance, so lifestyle modification at an early stage (lean NAFLD) is possible to inhibit progression to NASH and irreversible liver fibrosis.^[22] However, this remains to be analyzed with prospective studies.

Monitoring

Oniki K *et al.* in a Japanese population with an observation duration of 5.5 ± 1.1 years showed the PNPLA3 G / G genotype in normal BMI subjects was associated with a risk of NAFLD (OR 3.06; 95% CI 1.11-8.43, $p < 0.05$) and decreased eGFR (partial regression coefficients (SE) -3.26 (1.24), $p < 0.05$).^[10] It shows that subjects with normal BMI status accompanied by PNPLA3 G / G genotypic careers should be monitored more closely for NAFLD events, decreased kidney function, and other complications that arise. Information about the PNPLA3 genotype in normal BMI subjects is beneficial for prevention activities, although further research with large-scale subjects is needed to confirm the findings.

CONCLUSION

NAFLD should be considered as a differential diagnosis in normal BMI patients with abnormal liver enzymes. NAFLD indicates a high risk of metabolic abnormalities and/or cardiovascular morbidity. The rs738409 polymorphism in the PNPLA3 gene is a significant genetic factor of NAFLD and advanced liver disease, including hepatic steatosis, cirrhosis, and hepatocellular carcinoma. The rs738409 polymorphism is associated with decreased protein hydrolysis function and accumulation of hepatic triglycerides. Further research is needed to understand the pathogenesis, therapy, prognosis, and lean relationship of NAFLD with other diseases.

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Cite this as:

Fachrureza M, Pratomo B. Lean Non-Alcoholic Fatty Liver Disease (NAFLD). *Clinical and Research Journal in Internal Medicine*, 1.1 (2020): 46-54.

Fatty Liver Disease and Renal Function among Normal Weight Subjects. *PLoS ONE*. 2015; 10(7): e0132640. [DOI: 10.1371/journal.pone.0132640]

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