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MINIREVIEWS

Fatty liver without a large "belly": Magnified review of non-alcoholic fatty liver disease in non-obese patients

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is well described as a common cause of chronic liver disease, mostly in the obese population. It refers to a spectrum of chronic liver disease that starts with simple steatosis than progresses to nonalcoholic steatohepatitis and cirrhosis in patients without significant alcohol consumption. NAFLD in the non-obese population has been increasingly reported and studied recently. The pathogenesis of nonobese NAFLD is poorly understood and is related to genetic predisposition, most notably patatin-like phospholipase domain-containing 33 G allele polymorphism that leads to intrahepatic triglyceride accumulation and insulin resistance. Non-obese NAFLD is associated with components of metabolic syndrome and, especially, visceral obesity which seems to be an important etiological factor in this group. Dietary factors and, specifically, a high fructose diet seem to play a role. Cardiovascular events remain the main cause of mortality and morbidity in NAFLD, including in the non-obese population. There is not enough data regarding treatment in non-obese NAFLD patients, but similar to NAFLD in obese subjects, lifestyle changes that include dietary modification, physical activity, and weight loss remain the mainstay of treatment.

Key words: Nonobese; Nonalcoholic fatty liver disease; Hepatic steatosis; Nonalcoholic steatohepatitis; Genetic

Core tip: Nonobese nonalcoholic fatty liver disease (NAFLD) is likely a different entity than obese NAFLD, with its unique genetic predisposition. NAFLD in the nonobese population has been increasingly reported and studied recently. It is associated with components of metabolic syndrome. Interestingly, even though non-obese NAFLD patients have normal weight ranges, weight loss remains the mainstay treatment and was found to be beneficial. Diagnosis and treatment are similar to the obese non-alcoholic fatty liver disease. Further research is needed for better understanding of the genetic and environmental factors affecting the course of this specific entity.

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INTRODUCTION

With the growing epidemic of metabolic syndrome, nonalcoholic fatty liver disease (NAFLD), has become the most common cause of chronic liver disease in the Western world[1,2]. It is characterized by hepatic fat accumulation (steatosis) after excluding significant alcohol consumption; more than 21 drinks a week in men and 14 drinks a week in women[3,4], or more than 140 g weekly[2]. Disease spectrum ranges from hepatic steatosis, to nonalcoholic steatohepatitis (NASH), which is characterized by hepatic inflammation and hepatocyte ballooning. When advanced, NASH can progress to advanced fibrosis, cirrhosis, and hepatocellular carcinoma[5-7]. NAFLD is the most common cause of cryptogenic cirrhosis[8]. Occasionally, NAFLD can progress to hepatocellular carcinoma skipping cirrhosis interval[9]. NAFLD was first reported in 1980 by Ludwig *et al*[10] who described histological findings in 20 patients, mostly obese, with NAFLD. Obesity has been historically associated with NAFLD, however, not all obese patients develop NAFLD[11]. NAFLD is also reported in non-obese population[11-16]. NAFLD is a major cause of hepatic morbidity and mortality[17]. Here, we review basic and clinical features of non-obese NAFLD.

PREVALENCE

The prevalence of non-obese NAFLD using a cutoff body mass index (BMI) of 25 kg/m^2 ranges from 4.2% to 27.5%[11]. Using the national health and nutrition examination survey Ⅲ data collected from 1988-1994, the prevalence of non-obese hepatic steatosis in patients with BMI less than 25 kg/m^2, was 21%[11]. In a community-based study in Hong Kong, the prevalence of NAFLD was 19.3% and 60.5% in non-obese patients and obese patients respectively, using BMI of 25 kg/m^2[16]. This is comparable to the prevalence of obese NAFLD which, in most studies, ranges between 6.3%-30%[3].

PATHOGENESIS AND RISK FACTORS

Intrahepatic triglyceride content plays an integral role in the pathogenesis of non-obese NAFLD[18]. Hepatic steatosis is chemically defined as increased intrahepatic fatty acids content that are more than 5% of the liver weight[19], or histologically as 5% or more intrahepatic steatosis in a liver section[20-22]. There are multiple factors that increase intrahepatic free fatty acids. Increased release from the adipose tissue, and subsequent increase in the free fatty acid uptake by skeletal muscle and liver tissues, is noted in NAFLD patients. This is facilitated by alterations in the free fatty acid transport, specifically protein CD34, which regulates tissue free fatty acids uptake from plasma, and is found to have decreased expression in the adipose tissue, and increased expression in hepatic and skeletal muscle tissues in subjects with insulin resistance and intrahepatic steatosis[20].

Factors that lead to increased *de novo* synthesis, and decreased oxidation of free fatty acids in the liver, contribute to the mechanism for development of hepatic steatosis and progression. *De novo* synthesis and reduced free fatty acid oxidation processes are facilitated by sterol regulatory element binding protein and carbohydrate responsive element binding protein, both of which are stimulated by hyperglycemia and hyperinsulinemia[20,23,24]. It has been proven that in non-obese NAFLD, NASH incidence is higher when associated with polymorphism in the sterol regulatory element-binding factor-2 (*SREBF-2*) gene[25].

The excretion of intrahepatic free fatty acids from the liver as very low-density lipoprotein particles, VLDL-TG, is also increased, however the excretion rate plateaus eventually, and won't be able to cope with the increased production of free fatty acids, causing increased intrahepatic triglyceride storage[20].

In a study to determine the relationship between hepatic steatosis and insulin resistance[18], Korenblat *et al*[18] used an euglycemic hyperinsulinemic clamp procedure in 40 non-diabetic, obese patients. They used magnetic resonance spectroscopy to determine the intrahepatic triglyceride content, which ranged in their population study from 1% to 46%; they found that hepatic insulin sensitivity was inversely correlated with intrahepatic triglyceride content (r = 0.599, P < 0.001), insulin sensitivity on skeletal muscles and adipose tissue was also inversely correlated with intrahepatic triglyceride content (Skeletal muscle: r = -0.656; P < 0.001, adipose tissue: r = -0.590; P < 0.001). Intrahepatic triglyceride content was found to be the best predictor of insulin action on these tissues, independent of body mass index[18]. This study suggests that hepatic steatosis might not only be an outcome of insulin resistance and metabolic syndrome, but also a possible etiology of NAFLD regardless of BMI[18].

NAFLD is believed to be affected by the adipose tissue by the induction of inflammatory changes through releasing what is known as adipokines. Adiponectin, leptin, ghrelin, resistin, visfatin, retinol-binding protein 4 (RBP4) among many other adipokines been described[26]. Insulin resistance, obesity and type 2 diabetes mellitus are all risks for having low levels of adiponectin. Adiponectin secreted 50% less in NASH patients than normal individuals. Also, it can be correlated with NAFLD progression[26,27]. It is proposed that it has anti-inflammatory effects by induction of tumor necrotic factor-alpha (TNF-α) and interleukin-6 (IL-6) and inhibition of cytokine IL-10[27]. Leptin is believed to have the opposite correlation with regards

to its association with the amount of adipose tissue and also the effects on NAFLD. From studies that observed the results of leptin injection in animal, it is suggested that leptin increase levels of procollagen-I, transforming growth factor-β and TNF-α. This, in return, leads to both inflammatory escalation and progression of fibrosis. The relationship between leptin and NAFLD is not fully understood[26,28].

When it comes to the risk for developing non-obese NAFLD, it is the fat distribution rather than the total body fat that matters[29]. Specifically, visceral fat is more important risk factor than total body fat or waist circumference[11,30]. Subcutaneous fat acts as a reservoir of metabolically benign fat, however, visceral fat has been associated with insulin resistance, hypertriglyceridemia and low HDL[30]. Visceral fat is a rich source that can saturate portal vein with free fatty acids and pro-inflammatory cytokines, like TNF-α, IL-6, and CRP, and subsequently causes hepatic fat accumulation and subsequent liver injury[30,31]. This explains why Asians, who are known to have higher than average total body fat and visceral fat, have high prevalence of metabolic syndrome and NAFLD at lower body mass indices when compared to other races[32].

High fructose diets and beverages also seem to play an important role in the development of NAFLD, especially in the young and the non-obese[11,33,34]. Fructose is lipogenic, and proinflammatory, it is rapidly phosphorylated in the cells, causing intracellular ATP depletion, uric acid production and subsequent cellular injury[33]. In one cross-sectional study, and after adjusting for age, gender, body mass index, and total daily calorie intake, NAFLD was significantly associated with higher intake of soft drinks[34].

HISTOLOGY

The histology spectrum of non-obese NAFLD doesn't differ much from obese NAFLD[35]. NAFLD classified into simple steatosis and NASH. The later have necroinflammaotry changes along the finding of steatosis. More than 5% of steatosis involving of the hepatocyte required making the diagnosis. Although NAFLD patients typically show macrovesicular steatosis, microvesicular steatosis could also be observed in about 10% of the cases. According to the American Association for the Study of Liver Diseases Clinical Single Topic Conference on NASH in 2002, NASH finding were assigned to necessary component, usual but not necessary and may be present but not necessary for diagnosis. Hepatocellular ballooning, lobular inflammation and the earlier described steatosis are necessary for making NASH in the biopsy sample. Hepatocellular ballooning is identified when the hepatocyte is swollen with rarefied cytoplasm. The lobular inflammation is usually mixed with inflammatory cells and mild. Perisinusoidal fibrosis, hepatocellular glycogenated nuclei, lipogranulomas, acidophil bodies, fat cysts are usual finding but not needed to the diagnosis. Mallory-Denk bodies, iron deposition and megamitochondria may be present, but not necessary for diagnosis[36,37].

Brunt *et al*[38] grading of the steatohepatitis depend in the severity of the inflammatory changes and fat deposition. Grade 1, mild, will have steatosis up to 66 %, occasional ballooning in zone 3, scattered intralobular inflammation with or without mild portal inflammation. Grade 2, moderate, steatosis of any degree, obvious ballooning, intralobular chronic inflammation and mild to moderate portal inflammation. In Grade 3, severe, showing panacinar steatosis, ballooning and disarray obvious, in addition to similar intralobular and portal inflammation to grade 2. The extent of fibrosis what is evaluated in NAFLD staging. Focal or extensive perisinusoidal fibrosis is considered in stage 1, whereas, progression to periportal fibrosis is stage 2, bridging fibrosis is stage 3 and cirrhosis is stage 4[36,38].

It is suggested by some studies that non-obese NAFLD generally has less severe histological appearance, but this doesn't necessarily mean a better outcome[15]. In a Chinese prospective cohort study that included 307 NAFLD patients, 23.5% were non-obese and were found to have lower fibrosis stage (1.3 ± 1.5 *vs* 1.7 ± 1.4; $P = 0.004$), and liver stiffness measured by transient elastography (6.3 kg *vs* 8.6 kg; $P < 0.001$)[15]. In another study that involved 1090 patients with NAFLD confirmed by liver biopsy, the non-obese NAFLD cohort (11.5%) was found to have significantly lower degree of steatosis, and fibrosis, but more severe lobular inflammation; however, there was not much difference between two groups between hepatocyte ballooning and NASH[7].

GENETIC PREDISPOSITION

A genetic predisposition to non-obese NAFLD is undoubtedly present and different polymorphisms in genes that regulate lipid metabolism have been identified to play an integral role in development and progression of non-obese NAFLD[39]. It is a challenging task attempting to interpret associations from genome-wide association studies (GWAS) and elucidating the causal effect of the reported associated NAFLD variants[40]. We will attempt to focus our review on simplifying the following known NAFLD varients; patatin-like phospholipase domain-containing 3 (PNPLA3), SREBP-2, transmembrane 6 superfamily 2, and cholesterol ester transfer protein, and their role in development and progression in non-obese NAFLD.

Intrahepatic triglyceride accumulation that leads to hepatic insulin resistance, characterizes non-obese NAFLD, further impairs the ability of insulin to regulate hepatic glucose and VLDL production leading to hyperglycemia, hyperinsulinemia, hypertriglyceridemia, and a low HDL cholesterol concentration[18,41]. NAFLD in a non-obese population is not uncommon and GWAS have identified a single nucleotide polymorphisms (rs738409) in the patatin-like phospholipase domain-containing 3 (*PNPLA3*) gene with development of NAFLD[42]. PNPLA3 encodes a 481 amino acid protein expressed in the endoplasmic reticulum and at the surface of lipid droplets

in hepatocytes and adipocytes, and has acyl hydrolase activity, which plays a role in the hydrolysis of three major glycerolipids (*i.e*., triacylglycerol, diacylglycerol, and monoacylglycerol), leading to hepatic triglyceride accumulation[43].

A meta-analysis by Sookoian and Pirola, revealed that the G allele of rs738409 was associated with increased aminotransferase and severity of NAFLD in various ethnic groups, data also showed 73% higher liver fat content in populations with the G allele than weight-matched subjects homozygous for the C allele[44]. A study conducted by Romeo *et al*[45] showed that the risk allele (G-allele) of rs738409 was more prevalent in Hispanics compared to Europeans. The frequencies reported include 17% in African Americans, 23% in European descendants, 45% in Japanese and 49% in the Hispanic population, explaining a consistent fraction of the inter-ethnic variability in NAFLD susceptibility[45]. It has been observed that non-obese NAFLD subjects had higher G allele of rs738409 than obese NAFLD subjects and the identified risk allele is strongly associated with increased hepatic fat contents, hepatic inflammation, and elevated ALT levels[46]. Of important significance is the association between PNPLA3 G allele and liver fat contact being independent of insulin resistance and other metabolic comorbidities like obesity and dyslipidemia in non-obese population[47].

The *SREBF-2* gene codes for sterol regulatory element-binding protein-2 (SREBP-2), which is the nuclear transcription factor responsible for regulating genes involved in cholesterol synthesis, uptake, and excretion[25]. Altered cholesterol metabolism results in hepatic cholesterol accumulation and subsequent liver injury[48]. A study by Musso *et al*[25,49] has shown the polymorphism rs133291 C/T in the SREBF-2 gene can be used to predicted 7-year incidence of NAFLD in non-obese, and nondiabetic patients without metabolic syndrome at baseline. Histologically, it is observed that in biopsy proven non-obese NAFLD, NASH incidence is higher when it's associated with SREBF-2[25].

Also noteworthy is the newly NAFLD- associated gene variant on the transmembrane 6 superfamily 2 (*TM6SF2*) gene. A variant located in the *TM6SF2* gene, *rs58542926* encoding an amino acid substitution p. Glu167Lys (E167K), is associated with hepatic triglyceride content (HTGC). Research shows that the effect of rs58542926 on HTGC was independent of the effect mediated by rs738409, obesity, or insulin resistance[50]. The rs58542926 T allele (Lys167) has been observed to be associated with disease severity, suggesting that the variant might have a small effect on the risk of NASH. Unlike the overwhelming evidence of the role of PNPLA3 in the modulation of NAFLD and disease progression in different populations around the world, the initial finding of the effect of rs58542926 have not been reliably able to show such correlations. In a study conducted by Dongiovanni *et al*[51], they isolated increased risk of NASH and hepatic fibrosis in the presence of TM6SF-2 from its proposed cardiovascular protective role represented by TG protective response to insulin resistance[51].

Cholesterol ester transfer protein plays a role in transferring TG and cholesterol in between lipoproteins[52]. A well-known two single nucleotide polymorphisms (rs12447924) and (rs12597002) was postulated as a risk factor for NAFLD. More evidently, it was seen in between lean homozygotes and it was as high as 30%, compared to 10%-15% lean heterozygotes and 3%-5% lean wild[52].

CLINICAL AND METABOLIC FEATURES OF NON-OBESE NAFLD

Non-obese NAFLD is associated with components of metabolic syndrome. Some studies suggested lower prevalence of metabolic profile components in the non-obese NAFLD when compared to the obese NAFLD[53], on the other hand, other studies suggested similar or even higher prevalence of metabolic syndrome components in non-obese NAFLD[12,54]. In one retrospective study to determine the factors that are independently associated with non-obese NAFLD, using the national health and nutrition examination survey Ⅲ data between 1988 and 1994, NAFLD in both obese and non-obese, was correlated, when compared to control subjects, with age, Hispanic heritage, and with components of metabolic syndrome; visceral obesity, diabetes, hypertension and hyperlipidemia[53]. When comparing non-obese to obese NAFLD, the cohort was found to be younger, with lower prevalence of hyperlipidemia, hypertension, and diabetes. They also had less degree of elevated liver enzymes, specifically AST, and ALT[53].

Alam *et al*[12] evaluated 229 Indian patients with NAFLD by histology, and found that the non-obese population was metabolically similar to the obese, with no significant difference of levels of total cholesterol, triglycerides, HDL, blood glucose, ALT, AST, GGT, and insulin resistance. Kwon *et al*[54] non-NAFLD in 12% of 29994 selected cohort who underwent routine comprehensive health evaluations, he also found that non-obese women had higher adjusted prevalence rate of hypertension, hyperglycemia, hypertriglyceridemia and lower HDL, when compared to the obese woman[54].

In one longitudinal observational study that aimed to investigate the factors associated with the development and regression of NAFLD in non-obese NAFLD, using a cutoff body mass index (BMI) of 25 kg/m^2, and ultrasound as the diagnosis modality, among all factors of metabolic syndrome, and after adjusting for age, sex, baseline BMI and components of metabolic syndrome, triglyceride level above 150 mg/dL at baseline was significantly associated with the development and regression of NAFLD in the non-obese, ORs = 1.54 (1.10-2.14) and 0.60 (0.38-0.96)[14]. Body weight change was also significantly associated with development and regression of NAFLD in both obese ORs = 1.16 (1.09-1.24) and 0.69 (0.63-0.75) and non-obese ORs = 1.23 (1.17-1.30) and 0.74 (0.67-0.81). Other factors that were not significantly associated with progression and

regression of NAFLD in non-obese included fasting blood sugar more than 100 mg/dL, blood pressure more than 130/85 mmHg, HDL less than 40 mg/dL in male and less than 50 mg/dL in females[14].

Following a cohort of NAFLD patients diagnosed by biopsy for 15.7 years in Sweden revealed that the most common mortality cause was cardiovascular. Worth mentioning that 85% of the patients included in the study were overweight or obese at baseline[2]. There is no enough data about cardiovascular risk of non-obese NAFLD, but being a disease entity enriched with metabolic syndrome risk factors, cardiovascular events seem to remain the main cause of morbidity and mortality in such patents[2,55].

DIAGNOSIS

Diagnosing Non-obese NAFLD doesn't differ from obese-NAFLD, with liver biopsy continues to be the gold standard diagnostic modality and should be considered in populations with diagnostic uncertainty[4,56]. The importance of identifying NASH lays in identifying risk of advanced fibrosis, which could lead to cirrhosis and hepatocellular carcinoma[19]. Despite liver biopsy being the gold standard, it should be taken under consideration that up to 27% of NASH diagnosis could be missed from reading variability and from inadequate sample due to uneven disease involvement in the liver[57]. There are many non-invasive tools that can be useful for staging NAFLD patients. These tests also have the advantages of availability, and being cheap in addition to been non-invasive. Using Fibrosis 4 (FIB-4) index for advance fibrosis have negative predictive value (NPV) as high as 96% with using a liberal cutoff (1.3) and of 93% when using a more stricter cutoff of 2.7[58]. NAFLD fibrosis score also has comparable results.

Two physical modalities are more useful in getting accurate results. Transient elastography and magnetic resonance elastography. The latter is not widely available and has the disadvantage of been expensive. Transient elastography is particularly useful in non-obese NAFLD patients, given its limited utility on patient with BMI > 30 kg/m^2. In one large study, it was found to have NPV 99% and PPV 46% with a use 10.3 kPa as a cutoff for cirrhosis[11,58].

TREATMENT

Different pharmacological modalities have been investigated in the treatment of NAFLD and, so far, there is no evidence of effective therapy, life style modification remains the main stay of therapy[59]. An important mechanism of cellular injury in NASH is oxidative stress, and vitamin E has been investigated as a treatment option[60]. Vitamin E is currently recommended as a first line therapy in non-diabetic patients with NASH but not in diabetic patients, NAFLD without liver biopsy, NASH cirrhosis, or cryptogenic cirrhosis[3].

Obeticholic acid (OCA) showed evidence in improving fibrosis and decrease NAFLD score in NASH population[61]. In a large randomized, multicenter study obtained by Neuschwander-Tetri *et al*[61], OCA found to reduce fibrosis, NAFLD score and steatosis histology at the primary end point. Although their results were encouraging, there was no difference between treatment and placebo arms in terms of reversing NASH. Farnesoid X receptor activation by OCA are believed to reduce liver lipogenesis by down-regulating SREBP1c and up-regulating SIRT1 and this mechanism can play important role treating NASH[61]. However this could increase serum cholesterol by inhibiting cholesterol conversion to bile acid.

Interestingly, even though non-obese NAFLD patients have normal weight ranges, weight loss remains the mainstay treatment and was found to be beneficial. Shen *et al*[62] reported that weight loss and exercise has the greatest impact in treating NAFLD in patients with PNPLA3 GG genotype polymorphism, however the study was limited by lack of data on histological improvement as liver biopsies were not done. A study done by Jin *et al*[63] concluded that 10% cholesterol reduction and 5% weight loss cause 20% steatosis improvement in his liver donor cohort, including the non-obese and overweight subgroups.

Visceral fat, as mentioned earlier, is strongly associated with hepatic steatosis, and NASH in non-obese patients, and should be the focus for future intervention trials. In one randomized control trial, 50 morbidly obese patient were assigned to 2 groups, gastric bypass with or without surgical removal of the greater omentum; the combined intervention was found to cause much more significant improvement in insulin sensitivity[64]. This study can inspire further studies on the non-obese population to see if this can help improve the metabolic profile and reduce the risk of advanced liver disease in this subset of patients.

In one retrospective study that followed 619 NAFLD patients in the United States, Europe, and Thailand for more than 12 years, regardless of the other histological features, fibrosis stage was found to be the most important prognostic factor in NAFLD overall and liver-related mortality, liver transplantation, and liver-related events. The presence of diabetes, smoking, age, and lack of statin treatment, were the other factors found to affect long term survival as well in this study[65]. Not underestimating the importance of treating NAFLD patient to prevent fibrosis, but this study points to the importance of identifying this subset of patients, NALFLD with evidence of fibrosis, even in early stages, for an aggressive and comprehensive approach to lessen long-term effects.

CONCLUSION

Non-obese NAFLD is likely a different entity than obese NAFLD, with its unique genetic predisposition. It is associated with components of metabolic syndrome. Diagnosis and treatment are similar to the obese

NALFD, with weight loss still being the mainstay of the treatment. Further research is needed for better understanding of the genetic and environmental factors affecting the course of this specific entity.

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