Pharmacological and Non-Pharmacological Treatment in Non-Alcoholic Fatty Liver Disease

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) is a spectrum of liver disease, from steatosis to liver cirrhosis in individual who does not consume alcohol in significant amount. The prevalence of NAFLD in Indonesia was estimated around 30%, this condition related to the increased incidence of metabolic disorders. Current understanding of NAFLD pathogenesis is the third-hit theory, in which insulin resistance resulting in free fatty acid accumulation that triggers inflammation causing fibrosis and hepatocyte death, and these conditions are not followed by adequate hepatocyte proliferation.

Treatment of NAFLD requires both non-pharmacologic and pharmacologic interventions. Life style intervention includes restricting calories, low saturated fat and low sugar diet, and also physical activity. Bariatric surgery remains controversial since in several study participants had experienced deterioration of disease. There are no definitive treatment for NAFLD currently. Treatment is aimed to improved insulin sensitivity, decreased oxidative stress and inflammation. Several agents use for treatment of NAFLD are insulin sensitizer (metformin and glitazones), statin, omega-3, vitamin E, ursodeoxycholic acid, orlistat, pentoxyphylline, and losartan.

Keywords: *NAFLD, treatment, pharmacologic, non-pharmacologic*

ABSTRAK

Penyakit perlemakan hati non alkoholik (PPHNA) merupakan suatu spektrum penyakit hati dari steatosis hingga sirosis hati pada individu yang tidak mengkonsumsi alkohol dalam jumlah yang signifikan. Prevalensi PPHNA di Indonesia sekitar 30%, terkait dengan meningkatnya insiden penyakit metabolik. Patogenesis PPHNA yang kini berkembang adalah third-hit theory, dimana akibat resistensi insulin didapatkan akumulasi asam lemak bebas yang memicu inflamasi sehingga terjadi fibrosis dan kematian hepatosit yang tidak diimbangi dengan regenerasi hepatosit.

Pengobatan PPHNA memerlukan intervensi non-farmakologis dan farmakologis. Mulai dari melakukan perubahan gaya hidup dengan pembatasan kalori, diet rendah lemak jenuh dan rendah gula, serta aktivitas fisik. Pembedahan bariatrik masih menjadi kontroversi dalam tatalaksana pasien PPHNA, karena pada beberapa studi didapatkan beberapa subyek yang mengalami perburukan penyakit. Belum ada obat-obatan yang menjadi terapi definitif PPHNA, selain dengan melalui perbaikan sensitivitas insulin, menurunkan stres oksidatif dan inflamasi. Beberapa pengobatan farmakologis pada PPHNA dapat diberikan insulin sensitizer yaitu metformin dan glitazon, statin, omega-3, vitamin E, asam ursodeoksikolat, orlistat, pentoksifilin, dan losartan.

Kata kunci: *PPHNA, pengobatan, farmakologis, non-farmakologis*

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a spectrum of liver disease, from steatosis until cirrhosis in individual who does not consume alcohol in significant amount. NAFLD becomes a huge health problem in Asia Pacific countries, including Indonesia. A literature showed that there was quite high incidence of NAFLD in Indonesia, particularly about 30%.[1] High prevelance in various places is associated with the increase incidence of metabolic diseases, such as diabetes melitus, dyslipidemia, obesity, or metabolic syndrome.[1] NAFLD is also a risk factor for hepatocelullar carcinoma, therefore important to be managed.[2] For Asia Pacific countries, this burden is added with the high incidence of chronic viral hepatitis. The association between NAFLD and metabolic syndrome is related to insulin resistance.[3] In United States, it was obtained that 30.1 million individuals with obesity suffered from steatosis and 8.6 million suffered from steatohepatitis. Obesity becomes a separated risk factor for NAFLD, with 5 fold increased risk, diabetes melitus either type 1 or 2 becomes a dependant risk factor to the occurrence of NAFLD, as well as dyslipidemia and viceral adipocytosis, which all are part of metabolic syndrome.[4]

Pathogenesis of NAFLD and non-alcoholic steatohepatitis (NASH) alone cannot be explained precisely, several current known theories were two-hits model. The model was introduced by Day et al in 1998, where insulin resistance played important role in causing accumulation of triacylglycerol and free fatty acid, which then experienced oxidation and produced reactive oxygen species (ROS) and caused the occurrence of inflammatory response due to oxidative stress.[3] Till date, it still cannot be explained how NASH can happen in a person and not to the other person.[3,4]

Diagnosis of NAFLD is still a challenge for practitioner. Till current, liver biopsy is a gold standard for the establishment of diagnosis. Therefore, considering that the procedure is quite invasive, it is not performed often. In general, suspicion of NAFLD is based on the presence of abnormal liver function, in individual whose risk has been described above, so that NAFLD become the first possibility. However, in individual with normal liver function results, the possibility of NAFLD cannot be kept aside.[5]

PATHOGENESIS

Till date, theory which is still developing about pathogenesis of NAFLD and NASH is two-hit theory, however many factors are believed to play role in the occurrence of NAFLD and its progression. Metabolic syndrome and insulin resistance is a common condition found in NAFLD patients, however not all individual with insulin resistance develop NAFLD and vice versa, therefore other factors are also predicted to play role in the occurrence of NAFLD. Genetic factors associated to endogen anti-oxidants and fat distribution are suspected to play role in disease progression, where some experienced progression to NASH, but not in other individuals. Fat accumulation in hepatocytes, particularly in the form of triglycerides become the absolute requirement to the occurrence of NAFLD, however the primary metabolic disorder causing this is which involve many factors. Understanding NAFLD pathogenesis show that free fatty acid plays important role, and triglyceride is suspected to have protective role. Free fatty acid induces inflammation through nuclear factor-κB (*NF-κB)* and also causes mitochondria dysfunction. Other theory known as third-hit theory, is a modification of two-hit theory where post inflammation hepatocyte death happens, not balanced with regeneration.[5,6,7]

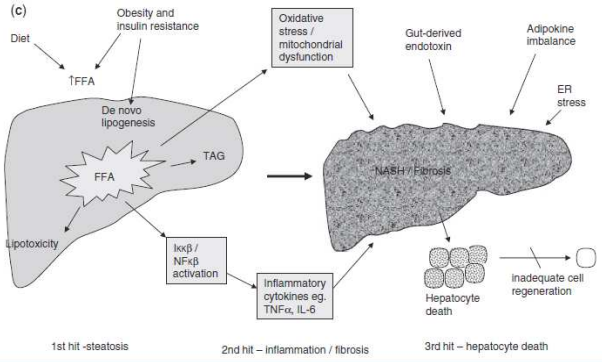

Figure 1. Pathogenesis of NAFLD based on third-hit theory[7]

Molecularly, lipid peroxidation happens as a result of oxidative stress through mitochondria dysfunction, P450 cytochrome activation, and iron overload. Oxidative stress causes cell impairment through the impairment of organelles, DNA and mtDNA through inflammation process mediated by NF-KB activation and IKB degradation. Inflammation that happens is also mediated by endoplasmic reticulum stress which also causes apoptosis, further exacerbated by necrosis, oxidative stress, and activation of NF-KB and other mitogenic pathway.[8]

Insulin play role in regulation of fatty acid metabolism, where 25% fatty acid originated from lipogenesis which is controlled by sterol regulatory element binding protein (SREBP) whose work is

mediated by insulin. In NAFLD, there is decrease level of double unsaturated fatty acid, particularly γ linolenat acid and increase of fatty acid level accompanied with decrease ability of fatty acid oxidation. Regulators contributing to this event, such as SREBP, peroxisome proliferator-activated receptor (PPAR), and farnesyl X receptor are mediated by insulin and adipositoxin effect.[8]

DIAGNOSIS

Liver biopsy becomes the gold standard in establishment of NAFLD diagnosis, particularly in differentiating pure steatosis and steatohepatitis. NAFLD is generally suspected in individual with transaminase elevation with no apparent reason and no history of alcohol consumption. Ultrasonography and other radiological modality may give typical appearance in NAFLD, however it is often inaccurate in determining degree of impairment, therefore biopsy still become gold standard.[6,9]

Several non-invasive techniques are developed for NAFLD evaluation, however there is none which has been well validated, including transient elastography, tissue inhibitor of metalloproteinase (TIMP)-1, hyaluronate acid and procollagen III type III n-peptide (PIIINP). Some of these modalities become component in non-invasive evaluation in the degree of NAFLD.[9]

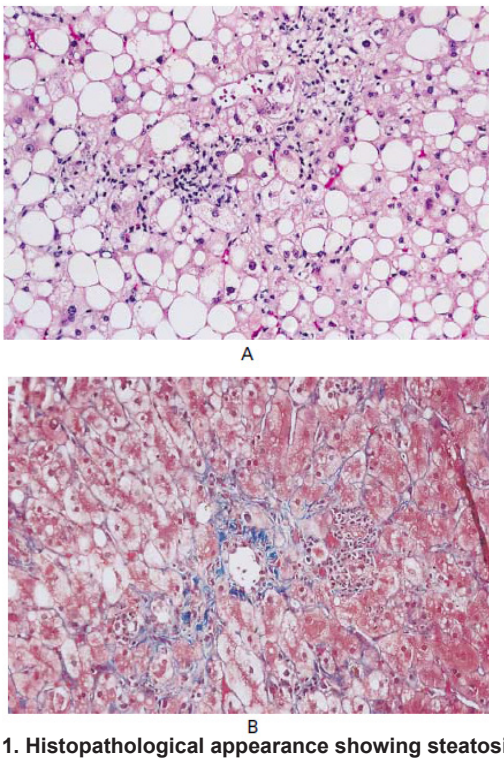

Figure 1. Histopathological appearance showing steatosis (A) and fibrosis (B)[6]

Table 1. Histopathological criteria in NAFLD[6]

Grading for steatosis
Grade 1, < 33% of hepatocytes affected
Grade 2, 33-66% of hepatocytes affected
Grade 3, > 66% of hepatocytes affected
Grading for steatohepatitis
Grade 1, mild
Steatosis: macrovesicular, involves up to 66% of lobules
Ballooning: occasionally found; zone 3 hepatocytes
Lobular inflammation: scattered and mild acute inflammation (polymorphonuclear cells) and occasional chronic inflammation (mononuclear cells)
Portal inflammation: none or mild
Grade 2, moderate
Steatosis: any degree; usually mixed macrovesicular and microvesicular
Ballooning: obvious and present in zone 3
Lobular inflammation: polymorphonuclear cells may be noted in association with ballooned hepatocytes; pericellular fibrosis; mild chronic inflammation may be seen
Portal inflammation: mild to moderate
Grade 3, severe
Steatosis: involves > 66% lobules (panacinar); commonly mixed steatosis
Ballooning: predominantly zone 3; marked
Lobular inflammation: scattered acute and chronic inflammation; polymorphonuclear cells may be concentrated in zone 3 areas of ballooning and perisinusoidal fibrosis
Portal inflammation: mild to moderate
Staging for fibrosis
Stage 1: zona 3 perivenular, perisinusoidal, or pericellular fibrosis; focal or extensive
Stage 2: as above, with focal or extensive periportal fibrosis
Stage 3: bridging fibrosis, focal or extensive
Stage 4: cirrhosis

TREATMENT

In principle, management of NAFLD also involves treating the associated comorbidity, such as obesity, diabetes, and dyslipidemia.

Non-pharmacological Treatment

- Life style intervention

  Several interventions which are believed to be beneficial for NAFLD patients, include aerobic exercise with the intensity equal to walking 30 minutes per day or 5 km per day 3 times a week, calorie restriction up to 30 kcal/kg/day with lower composition of saturated and trans fatty acid, also simple sugar, decrease of 10% body weight in 6 months and not so fast because it may aggrevate NAFLD. Life style modification is also adjusted to the existing comorbidities, particularly cardiovascular problem, the most common cause of death in NAFLD patients was coronary heart disease, where frequently dyslipidemia, obesity, and diabetes condition were found, and diabetes is a risk factor of cardiovascular disease. NAFLD also increases the risk of cardiovascular problem through inflammation process.[10]

A study by Bhat et al, in which 60 NAFLD patients were involved in India, showed that routine physical activity for 30 minutes a day with frequency of 5 times a week can decrease transaminase level and also improve histological appearance in 6 months evaluation.[11] Several population studies stated that in NAFLD patients, there was lower omega-3 consumption, higher omega-6 consumption, and also higher amount of cholesterol and saturated fatty acid, and less consumption of some vitamins, such as: ascorbic acid, tocopherol, and fiber. Meanwhile a study using 1,000 mg/day and 2,700 mg/day omega-3 in NAFLD patients revealed that omega-3 decrease ALT, improve the degree of perlemakan in ultrasound, and improve histological appearance, however the number of samples included were 42 and 23 patients.[12]

Alcohol consumption is known as risk factor of liver impairment, however in small amount several studies exhibited the opposite effect. The American Association for the Study of Liver Disease (AASLD) recommend NAFLD patients to not consume alcohol in large amount, which is 4 times per day or 14 times per week for male and 3 times per day or 7 times per week for female.[9]

- Bariatric surgery

  Ninety percent patients who undergo bariatric surgery will suffer from NAFLD, however this procedure is one of the choices in treating NAFLD. A study by Mathurin which was cited in the guidelines by American Association for the Study of Liver Disease (AASLD), showed the incidence of NAFLD decrease in obese individuals who undergo bariatric surgery, and in individuals with NAFLD or NASH, there was histological improvement in one or five years after surgery. AASLD does not contraindicate bariatric surgery in obesity individuals with NAFLD or NASH as long as cirrhosis has not happened.[9]

  Chavez et al, in their publication in Cochrane Review concluding from several prospective and retrospective cohort, stated that bariatric surgery revealed improvement of steatosis and inflammatory degree, however some publications reported the disease worsening in several individuals, but randomized control trial (RCT) on the role bariatric surgery was still lacking.[13]

  Publication by Younossi showed that bariatric surgery improve output of cardiovascular risk factors, although not specifically stating parameter of improvement in liver impairment, improvement of diabetes, dyslipidemia decrease the degree of liver impairment, also showed NASH improvement in 82% patients who undergo laparascopic adjustable gastric banding.[14]

Pharmacological Treatment

Several drug groups which can be used in NAFLD treatment based on AASLD guidelines and several studies reported some drugs commonly used were insulin sensitizer, statin, omega-3, vitamin E, ursodeoxycolate acid, orlistat, pentoksifilin, losartan.[9,15]

- Metformin

  Metformin is a drug from the insulin sensitizer group, where this drug can be used because insulin resistance is known to have role in the pathogenesis of NAFLD. Several studies showed that metformin improve insulin resistance in NAFLD patients and also improve transaminase. Some studies which use metformin include treatment of NAFLD in children (TONIC) study, this study compare metformin and vitamin E, both decrease aminotransferase level, however vitamin E is better in improving histopathological appearance in NASH. Other studies by Larine et al and Bugianessi et al, in year 2005 revealed that metformin 2 g/day improve aminotransferase better compared to vitamin E.[16,17] Garinis et al conducted RCT in 50 NAFLD patients comparing metformin and hypocaloric (decrease 500 kcal per day) and hypocaloric diet only, obtained improvement in ultrasound results in the group which received metformin ($p < 0.0001$).[18] Haukeland et al compared administration of metformin and placebo in 48 patients and obtained insignificant result in histological appearance of those patients.[19]

  Other studies by Nadeau et al comparing metformin and placebo in 55 NAFLD patients, there was no significant difference through ultrasound.[20] Study by Shields et al comparing 19 NAFLD patients receiving metformin 500 mg uptitrated to 1,000 mg with diet and exercise or diet and exercise alone, showed improvement in histological appearance.[21]

- Glitazone

  Glitazone, is an insulin sensitizer working in skeletal muscle and liver, increasing glucose uptake by improving peripheral insulin resistance. First drug from this group is troglitazone, however there is no study which use this drug. Troglitazone has higher hepatotoxic side effect compared to the following two drugs, particularly rosiglitazone dan pioglitazone.[22]

Aithal et al performed an RCT in 74 non-DM patients who have been proven to suffer from NASH through histology and ultrasound, patients received pioglitazone 30 mg and plasebo, results showed pioglitazone improve hepatocelullar impairment, but not for other parameter.[23] Belfort et al in 2006 compare pioglitazone 30 mg uptitrated up to 45 mg with placebo, both groups received low calorie diet, through histology there was significant improvement in steatosis, necroinflammation and fibrosis in group receiving pioglitazone.[24]

Sanyal et al conducted two studies; initial study in 2004 compared pioglitazone 30 mg and vitamin E 400 IU, concluded that there was inflammation improvement in both groups. The following study in 2010, Sanyal performed RCT to 247 patients comparing vitamin E, pioglitazone and placebo, observation was conducted for 96 weeks, resulted in histological improvement in vitamin E and pioglitazone groups.[25,26]

Other group of glitazone, which is rosiglitazone is said to improve degree of NAFLD better compared to metformin, however both combination has better effects compared to single administration.[27]

In histological evaluation, rosiglitazone inhibit hepatocytes ballooning, portal inflammation and fibrosis overall compared to placebo.[28]

- Omega-3

  Omega-3 improve lipid metabolism in liver, as regulator of transcription factors such as peroxisome-poliferator-activated receptor (PPAR), sterol receptor element binding protein (SREBP-1), and carbohydrate responsive element building (ChERBP) which have role in the progression of NAFLD to NASH.[29]

  In their publication in 2012, Di Minno et al reviewed 7 studies on the use of omega-3 in NAFLD, from those 7 studies, several performed randomization, however the number of subjects included in the studies were not big and the dose being used varied.[30] Those studies showed that omega-3 improved transaminase and liver profiles, several studies measure homeostatic model assessment insulin resistance (HOMA IR) and showed improvement.[29]

  Other meta-analysis and systematic review revealed that supplementation of polyunsaturated fatty acid (PUFA) gave effect to the biochemistry parameter, such as accumulation of liver fat and transaminase, however if performing meta-analysis towards RCT, there was no significant improvement in transaminase. In this review the dose of omega-3 seemed to give significant difference, however the duration of administration was more influential. Minimal dose needed to gave effect was $\geq$ 0.83 mg/day. Beside improving transaminase, omega-3 has cardio-metabolic effect which often found in NAFLD patients, such as: insulin resistance, diabetes, dyslipidemia.[31]

- Ursodeoxycholic acid

  Ursodeoxycholic acid (UDCA) has anti-inflammation, anti-oxidant, and antifibrosis effect and can improve liver impairment.[32] Studies on the administration of conventional and high dose ursodeoxycholic acid, most showed transaminase and histological improvement. However, one RCT with large sample size showed that UDCA did not improve the histologic appearance of NAFLD.[9] A study by Ratziu et al involving 126 subjects with NASH which had been proved through biopsy and experienced elevation of transaminase, were given high dose of UDCA 28-35 mg/kg/day, the results were patient experienced improvement of transaminase and also decreasing fibrosis marker level in the serum.[32]

- Statin

  NAFLD is closely associated with the presence of dyslipidemia, where statin is the most commonly used treatment in dyslipidemia through its effect inhibiting cholesterol synthesis through HMG-coA-reduktase inhibition. However, statin is suspected to have other effects in NAFLD treatment, particularly anti-inflammatory and anti-fibrosis. Statin is known may cause transaminase elevation, therefore its use in NAFLD is controversial.[33]

  Studies on statin administration in NAFLD are still limited, statin type, dose, duration, number of participating samples, there is no RCT with quite big sample size. However, studies which use statin, showed satisfying results.[34] In 2010, Hyogo et al performed a study to 43 dyslipidemia patients, who were given atorvastatin 10 mg and in the evaluation of biochemistry marker for NASH, improvement was reported. This was in line with the previous study. This effect is obtained because statin has TNF-α inhibition effect.[31,35] There is no RCT to evaluate the effect of statin administration to histopathological appearance, the use of statin alone becomes controversial because in several patients, there was elevation of transaminase level, however the incidence of severe liver dysfunction was very rare. Some publications and also AASLD

in its guidelines in 2012 stated that statin was safe to be used in patients with liver dysfunction and in patients with chronic liver disease (including NAFLD and NASH) the increase risk of drug induced liver disease (DILI) was not proven.[9,36]

- Vitamin E

  AASLD guidelines stated that study on vitamin E in NASH is still limited, both in the quantity and strength of the results. Two large studies on the use of vitamin E in NAFLD were pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis (PIVENS) dan treatment of NAFLD in children (TONIC). PIVENS compared pioglitazone, vitamin E, and plasebo by randomization of 247 adult patients with NASH and did not suffer from diabetes mellitus (DM). Eighty patients received pioglitazone 30 mg, 84 received vitamin E 800 IU, and the rest received placebo. Both gace significant results if compared with placebo in terms of decrease of transaminase level, steatosis improvement, however not in fibrosis score. While vitamin E is more superior compared to pioglitazone in NASH resolution. This study also reported that cardiovascular incidence was insignificantly different in three groups, where this became an issue in the use of high dose vitamin E.[9,37]

  TONIC study, compared vitamin E 400 IU twice daily, metformin 500 mg twice daily, and placebo in 175 children aged 8–17 year old. These three groups equally experience transaminase improvement, however in the group which received metformin, decrease of transaminase achieved earlier, which is in the first 24 weeks. In terms of histologic improvement, vitamin E is better in NASH resolution, particularly improve ballooning (44%), improve NASH score (41%), but does not effect to steatosis, fibrosis and inflammation. While metformin only improve ballooning (21%). The results of this study is also in line with smaller study by Bugianesi et al, as has been discussed above where vitamin E improve histologic appearance compared to metformin.[17]

  Other study by Akcam et al in 2011, comparing metformin and vitamin E, in this study metformin was reported to be better in improving steatosis in ultrasound, however this study only involved 67 patients.[38]

- Anti-TNF

  The development of second-hit theory where inflammation further had role in the progression of NAFLD to NASH, resulted in the idea to use anti-TNF. TNF-α as a pro-inflammatory cytokine plays role in stimulating hepatic stellate cells in matrix remodelling, further there was suspect in bacteria translocation which has role in causing further inflammation also support the use of anti-TNF in inhibiting progression of NAFLD. One of the drugs which has been tried is pentoksifilin which has anti-TNF effect, study showed improvement of transaminase level in 12 months and histologic improvement in 55% patients, however this study only involved 18 patients.[39,40]

  There has been no study which specifically use anti-TNF, such as: entanercept, infliximab or adalimumab in NAFLD patients, however a study in psoriasis, metabolic syndrome, and NAFLD patients using entanercept involving 89 patients, showed improvement in transaminase, CRP, fasting insulin level, HOMA index in 24 weeks, however in this study, NAFLD diagnosis is only established based on ultrasound.[41]

CONCLUSION

Until now, there is no single drug which can be used as definitive therapy in NAFLD. Medications which is used based on the pathophysiology include: (1) insulin resistance, (2) oxidative stress, and (3) inflammation. However, there is no clinical trial with quite big sample size which can be used as guideline in choosing therapy for NAFLD. Several existing studies and with quite big sample size, vitamin E and insulin sensitizer group can be used in the management of NASH to improve histological appearance. In the management of NAFLD or NASH, it need to be noted the presence of risk factors, comorbidity, and patients' adherence. Managing and controling risk factors are important in the management of NAFLD; presence of comorbidity can be a consideration in choosing treatment in NAFLD.

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