"Recent Advance in treatment of Non Alcoholic fatty liver Disease"

A PROJECT SUBMITTED TO

NIRMA UNIVERSITY

In partial fulfillment of the requirements for the degree of

Bachelor of Pharmacy

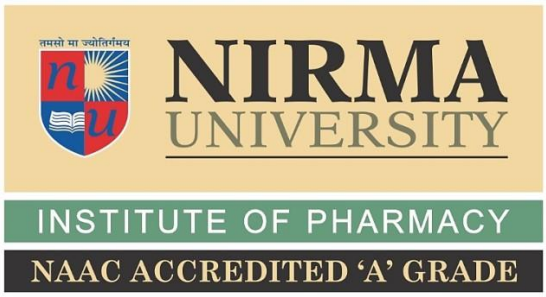
BY

PRINCE RATHOD A. (14BPH067)

Semester VIII

UNDER THE GUIDANCE OF

DR. SNEHAL PATEL



INSTITUTE OF PHARMACY

NIRMA UNIVERSITY

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GUJARAT, INDIA

APRIL 2020

Recent advance in treatment of Non Alcoholic fatty liver Disease

CERTIFICATE

*This is to certify that **"RECENT ADVANCE IN TREATMENT OF NON ALCOHOLIC FATTY LIVER DISEASE"** is the bonafide work carried out by **PRINCE RATHOD** (14BPH067), B.Pharm semester VIII under our guidance and supervision in the Institute of Pharmacy, Nirma University, Ahmedabad during the academic year 20__-20___. This work is up to my satisfaction.*

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DECLARATION

*I, **PRINCE RATHOD (14BPH067)**, student of VIIIth Semester of B.Pharm at Institute of Pharmacy, Nirma University, hereby declare that my project entitled "**RECENT ADVANCE IN TREATMENT OF NON ALCOHOLIC FATTY LIVER DISEASE"** is a result of culmination of my sincere efforts. I declare that the submitted project is done solely by me and to the best of my knowledge, no such work is done by any other person for the award of degree or diploma or for any other means. I also declare that all the information was collected from various primary sources (journals, patents, etc.) has been duly acknowledged in this project report.*

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"THE ROOTS OF EDUCATION ARE BITTER, BUT THE FRUIT IS SWEET"

Success does not lie in Results, but in efforts, being the best is not so important, doing the best is all that matters. Hence this acknowledgement is need to aware of what others are doing, applaud their efforts, acknowledge their successes, and encourage them in their pursuits. When we all help one another, everybody wins.

I would like to extend my sincere thanks to ***Dr Snehal patel (Guide),*** *Professor & Head at Department of Pharmacology, Institute of Pharmacy, Nirma University for their inspiration guidance, affectionate support and continuous encouragement given by them time to time in my completion of project work and also take this opportunity to place on record my hearty thank you for your perfect logistic support throughout this period of my project work.*

I also take this prospect to express a profound sense of appreciation to ***Dr. Manjunath Ghate,*** *Director Institute of Pharmacy, Nirma University, for providing world class Facilities and Environment to pursue this work and great ease.*

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Recent advance in treatment of Non Alcoholic fatty liver Disease

Abstract

In the developed world, the most common disease in the liver that affects up to a third of people is non-alcoholic fatty liver disease (NAFLD). It is closely linked to metabolic symptoms , particularly obesity and diabetes. This is a growing symptom for cirrhosis, liver-cell carcinoma and hepatic failure. Dietary and genetic factors decide the vulnerability and development of NAFLD. NAFLD can also be involved in cardiovascular disease pathogenesis. Some patients with irregular liver blood tests found by the way. Usually, care is one of exclusion. For the staging of disease, Liver biopsy is important, however new imaging methods and biomarkers arise which can ultimately play their part. NAFLD treatment is not yet firmly based on evidence. The treatment is actually designed to treat elements of metabolic syndrome which may be useful for the liver. The recent clarification of the progressive disease pathways shows a number of new goals worth explored in NAFLD animal models and subsequently in pilot studies.

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Recent advance in treatment of Non Alcoholic fatty liver Disease

INTRODUCTION:

In the absence of excessive alcohol use, NAFLD is characterized by unusual accumulation of insulin-related fat in liver NAFLD is a continum of non-alcoholic fatty hepatitis (NNAFL) liver abnormalities .The fatty accumulation (hepatic steatosis), starts with these diseases. The liver can remain fatty without affecting the liver function (NAFL), but steatosis is associated with inflammation and sometimes fibrosis by various mechanisms and insults in the liver.

As NAFLD 's progression of obesity, insulin and, ultimately, type 2 diabetes mellitus is optimistic, the hepatic manifestation of metabolic syndrome is also regarded as the ,This condition has not provided any pharmacologic treatment yet. The only proven approach is to provide lifestyle recommendations that can lead to continued weight loss in most patients with NAFLD presumptive or confirmed. Because of the involvement of NAFLD pathogensis in insulin resistance, oxidative stress, inflammation, and necroapoptosis, all possible therapeutic agents appear to have to target one or more of those pathological events.

Two forms of non-alcoholic fatty hepatitis, including liver inflammation, occur (NAFL) and non-alcoholic (NASH) steatohepatites.

Treatment is divided into two categories:

(1) steatosis (2)pathogenesis of progression

Steatosis resistance therapy Steatosis treatment is inexorably linked to obesity, insulin resistance and dyslipidemia. In general, weigh loss or pharmacological therapy directed towards insulin resistance or dyslipidemia are factors that decrease steatosis. Non-alcoholic Disease is also treated by Dietary Supplements like Vitamin E and vitamin C, Resveratrol, Anthocyanin, Green tea extract, Coffee, Garlic, Ginger.

Other than that Pharmacological therapy includes Thiazolidinediones, Pioglitazone, Rosiglitazone, Metformin, Statins, Fibric acid derivatives.

Epidemiology

NAFLD is often an asymptomatic condition with regular liver blood tests. Prevalence studies have been extremely complex, relying mostly Ultrasound that is proven to be active even when more than one-third of the liver is compromised by steatosis. In Western adults and 15 per cent in Asians, the NAFLD

prevalence appears to be around 20-30 per cent. The true incidence of NAFLD is not well defined due to the lack of prospective studies, although it appears to be low from the available information. Since liver biopsy is the only way to diagnose steatohepatitis accurately, NASH studies of incidence / prevalence are rare. According to available evidence, NASH is much rarer than NAFLD and affects 2–3% of the general population.

The presence and severity of obesity are strongly associated with NAFLD and NASH. Bariatric surgery studies reported in severe obese people (BMI > 35 kg / m2). 91% and 37% prevalence of NAFLD and NASH, respectively, while post-mortem studies reported that NASH. A recent observational study found that while central obesity is associated with inflammation frequency, dorsocervical lipohypertrophy is related with hepatocyte injury, inflammation and fibrosis in 3 % of patients with no obesity, 19% in obese patients and 50% in morbid obesity.

The other important association of Type 2 diabetes mellitus (T2DM) of the NAFLD has just been documented to reflect an ultrasound study of approximately 3000 non-selected patients with T2DM with prevalence of 70 percent. NAFLD is closely linked to other metabolic characteristics even in the absence of obesity and T2DM, with one NAFLD non-diabetes study showing that 18% of average weight patients and 67% of obessive metabolic requirements. There is no accurate data on temporary changes in NAFLD prevalence , Nevertheless, the increasing Obesity, diabetes and metabolic syndrome prevalence tend to constitute an increasing prevalence of NAFLD.

This phenomenon is of particular concern in the pediatric population, which is sure to lead to a greater incidence and prevalence of NAFLD in future as a result of the recorded increase in obesity. Up to now., children's Research have demonstrated a NAFLD Promotion of 3% in the general pediatric population and 53% in obese children. Reports of infants with NAFLD and children with NAFLD-related cirrhosis in primary school are clearly a cause of alarm.

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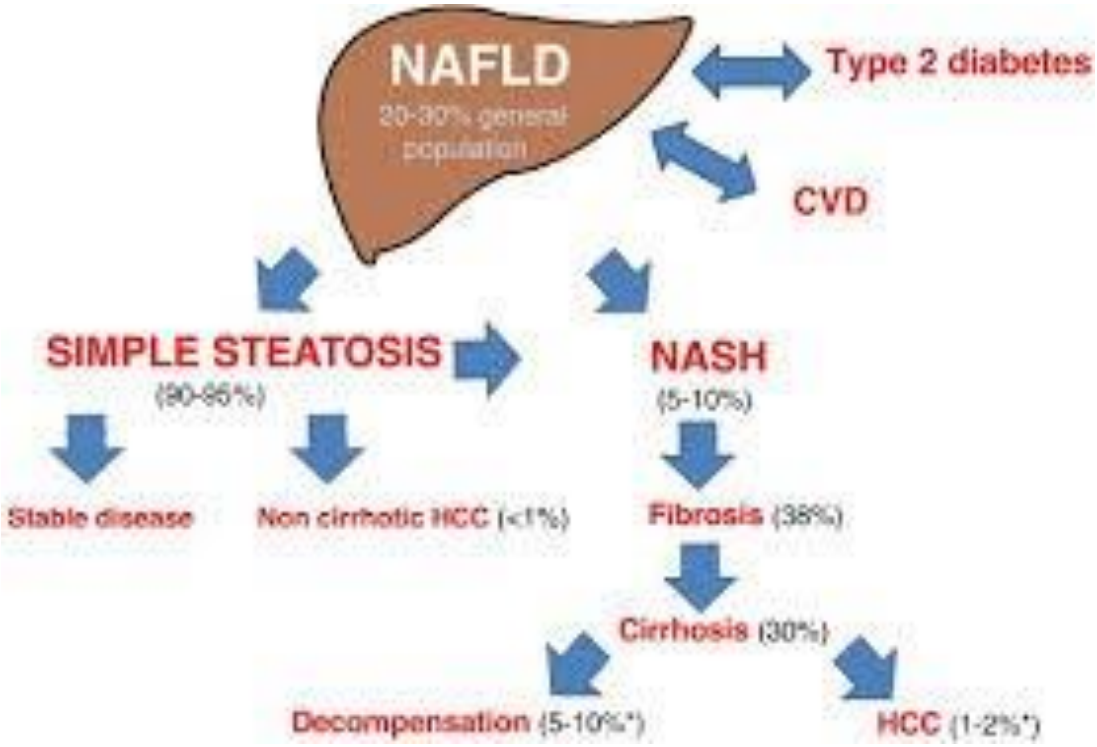
Susceptibility



Although most people with obesity, are insulin resistant and have metabolic syndrome Steatosis, steatohepatitis, fibrosis and cirrhosis will never occur in a minority. NAFLD's Potential environmental factors are nutritional and bacterial overgrowth of small intestines. Recent studies have shown that saturated fat, soft drinking, meat and meat diets are high and low. Although there is no question of an increased obesity preventing heavy drunkenness, evidence appears suggesting that "sensitive" light alcohol intake may protect against NAFLD / NASH, which is likely to be due to the beneficial effect of light alcohol consumption on heavy drinkers. The increased risk for NAFLDs and NASHs is related to antioxidants and omega 3-containing fish insulin sensitivity. Family research and differences in inter-ethnic susceptibility show that genetic factors can be important for the determination of disease risk. Although there has been no confirmation of advanced genetic associations in large studies with NAFLD, preliminary data suggest that polymorphisms in genes encoding triglyceride microsomal transmission proteins, transmission of phosphatidylethanolamine, dismutase superoxide 2. an rise in steate and / or fibrosis risk may be associated with the CD14 endotoxin receptor, TNFa, TGFb and angiotensinogen. It

seems likely that genes contributing to inherited susceptibility to this common disease will be identified in the near future with the advent of high-throughput gene analyzes and the reduced cost of whole genome wide scans.

PATHOGENESIS

There was a significant volume of literature, providing basis for understanding NAFLD's pathogenesis. As caloric intake increases and Composition of diet changes, Calories are high retained as adipose fat and cause microbiome changes, too. It Causes improvements Activation of innate immune systems, and an inflammation of adipose tissue in the bowel permeability and increasing systemic exposure of microbial intestinal products. The metabolism is the development of a condition insulin resistant. The insulin resistant mode which leads to increased lipolysis along with excess calorie intake provides an improved lipotoxic burden with excess carbohydrates, including free lipid acids in the liver. The de novo lipogenesis is further exacerbated, caused by hyperinsulinemia, which retained sensitivity to the lipogenic effects of insulin in a state otherwise resistant to insulin. The Liver tries to react through increased lipid oxidation and lipid exports; Excess lipids accumulate in lipid droplets that form a fatty liver when lipid accumulation and synthesis exceeds their metabolism and exports. Recently it has been shown that PNPLA3 protein builds up on lipid goplet surfaces. Proteasomal deficiency causes these accumulation under conditions of lipotoxic stress, where impaired lipolysis in Further fat accumulation is caused by those with PNPLA3 mutant. But how steatohepatitis and cirrhosis are caused by mutation development can not be explained. Cell stress, including oxidative stress and exposed proteins, can cause apoptosis, cell death and inflammation. In cells too, apoptosis can trigger renewable activity. There is still a lack of knowledge of the biological processes that cause cel death and inflammation, although much is known as lipotoximity. Fibrogenic remodeling of the liver causes prolonged inflammation. Recently important developments have been made in the development of NASH in vivo and in vitro models. Criteria for validating these models as human NASH models are more simple. When analyzing data from these models to understand it is critical that human disease decides whether such validations have been carried out in the model. Whether the composition of macronutrient represents human diet or whether human features such as obesity and systemic inflammating are normal in humans, or if they include dyslipidemia, insulin resistance, steatohepatitis and fibrosis, cell-signaling, transcriptomal harmony, etc.

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Potential therapeutic targets for nonalcoholic fatty liver disease.

Target	***Treatment***
Obesity	*Weight loss* • *Lifestyle modification* • *Medications* • *Orlistat, sibutramine* • *Bariatric surgery*
Insulin resistance	*Insulin sensitizers* • *Metformin, Thiazolidinediones (TZDs)*
Dyslipidaemia	*Lipid lowering agents* • *Statins, Fibrates, Polyunsaturated fatty acids*
Oxidative stress	*Antioxidants* • *Vitamins E and C, Betaine, N-acetylcysteine* *Probiotics* • *VSL#3, Oligofructose* *Venesection*
Cellular apoptosis	*Cytoprotective agents* • *Ursodeoxycholic acid (UDCA), Lecithin*
Pro-inflammatory cytokines	*Anti-tumour necrosis factor alpha agents*

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Target	*Treatment*
	• *Pentoxifylline*
End-stage liver failure	*Transplantation*
Other	*Novel treatments* • *Angiotensin receptor blockers (ARBs)* • *Incretin hormones* • *Sulfonylureas*

<u>NATURAL HISTORY AND OUTCOMES OF NON ALCOHOLIC FATTY LIVER DISEASE</u>

Many of the natural history data from NAFLD are based on indirect evidence from a limited population. Due to NAFLD's high incidence, only a fraction of NAFLD patients experience severe fibrosis or the resulting morbidity. The explanation for this is partly subtle variations in individual genetics, which alter the response to environmental and lifestyle influences, thus deciding the disease phenotype. A slightly higher mortality in NAFLD in general, compared with the general population, has been shown in recent findings from population research in Olmsted County; mortality and liver-related death from referral centers have been less than before recorded. Mortality Glucose intolerance / diabetes and higher age is associated with prevalence of cirrhosis in these patients. In patients with NAFLD in descending order, the top three leading causes of death are cardiovascular disease, cancer and liver disease. The risk for a patient to progress advanced hepatic illness, like hepatic and HCC decompenses, is greater If they are NASH patients than if they are NAFLD patients. Recent studies have shown that NAFLD may evolve with advanced NASH fibrosis, so it may not be a fully benign disease. Recently, an index liver biopsy found that 44% of patients with NAFLD had progressed to NASH, and 37% had advanced to fibrosis, including 22% to advanced stages. NAFLD management requires a significantly increased level of health care, especially after cirrhosis develops, as fibrosis deteriorates. While NAFLD incidence and the burden of disease in the years to come do not have exact models, the changing trends in obesity and DM suggest that this problem is on the rise worldwide and will make health systems more stressful.

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Recent advance in treatment of Non Alcoholic fatty liver Disease

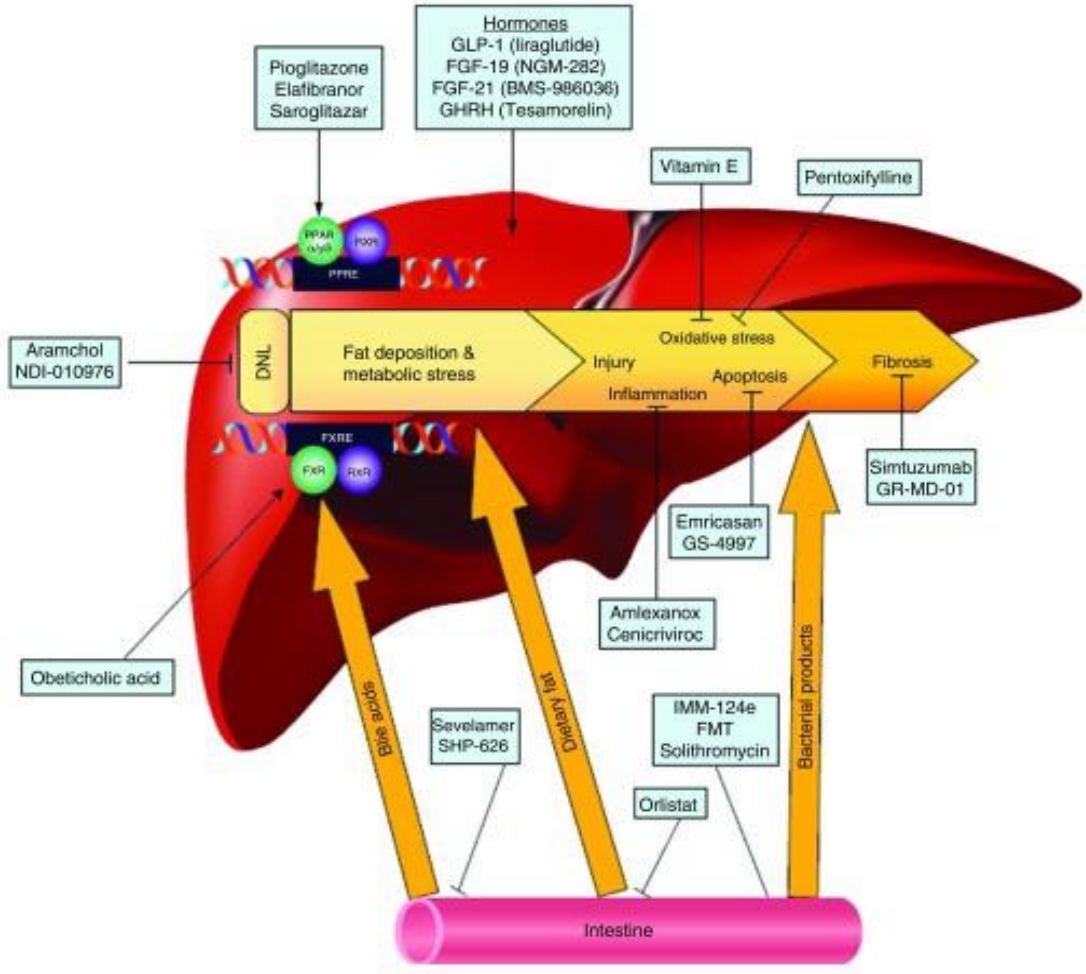
DIAGNOSIS

The condition is only suspected when liver functions have been found irregular in biochemical or hepatic imagery (ultrasonography, CT, or liver MRI), when it is done for another reason. NAFLD remains in large proportion of patients and is suspected to cause fatty liver. The gold standard NAFLD for diagnostic evaluation remains liver biopsy. The histological scoring system was the most commonly used in the past by NASH Clinical Research Network, reflecting a validated NAFLD activity score (NAS) scoring system. NASH is often considered to be 5 or more, and NASH is also not considered to be less than 3. NAS can not be used to replace prejudice NASH-NAFLD, although it is useful for histological diagnosis. As NAFLD is strong, it is not feasible to diagnose fibrosis-cirrhosis with liver biopsy. The accuracy of liver biopsy in determining fibrosis has also been challenged because of sampling errors and inter-observer variability that can result in over- or under-staging. Price, organizational problems and variations in histology reporting between and within the observer main disadvantages of liver biopsy and are therefore not generally used in clinical practice, particularly where other specific diagnoses need to be omitted. Alternative new approaches for the non-invasive fibrosis assessment have taken increasing interest in the past decade. Such techniques include two distinct but complementary approaches: serum biomarker calculation or hepatic stiffness estimation use transient elastography (TE) ultrasound-based elastography precursor. THE, Fibrosis Index (FIB-4), and NAFLD fibrosis scores are the best validated non-invasive tests in NAFLD-patients. For example, in recent meta-analyses based on 64 studies with a total of 13,046 NAFLD, the summary AUROC values for TE, FIB-4, and NAFLD for diagnosis of severe fibrosis-cirrhosis were 0.88, 0.84, and 0.84. if all three were assessed head-to - head, TE was most successful in diagnosing cirrhosis. Finally, Recent results indicate the accurate classifications of the subgroup of NAFLD patients at a high risk for developing liver complications and hepatitis transplant in non-invasive studies, including FIB- 4 and NAFLD fibrosis ratings, as well as TE related hepatitis stiffness measurements. For many NAFLD patients liver enzymes will often be normal. While several biochemical markers have been suggested for use of the previous NAFLD / NASH prediction such as TNF-a, IL-6, CRP, ferritin, enzyme serum prolideasis, advanced glycation end product soluble receptor, and Cytokeratin-18,none of these markers have demonstrated adequate sensitivity Or the accuracy of daily clinical test procedure. The Main modalities of imaging for clinical practice diagnosing NAFLD are ultrasonography, CT, and liver MRI. In general, to diagnose NAFLD, approximately 30 per cent of cases Sonography may involve liver steatosis. TE is an ultrasound imaging technique designed to evaluate the level of fibrosis in patients with NAFLD and NASH. The sensitivity and specificity of TE to diagnose different stages of

fibrosis was 79-92% and 75-92% respectively. Recent research also indicates that the value of the ultrasonic controlled attenuation parameter used in the TE technique can predict the degree of steatosis in NAFLD patients. A fraction of MRI protein dentity fat is the gold standard for non-invasive hepatic steatosis assessment. New MRI techniques such as MR elastography can non-invasively stage the degree of fibrosis in the diagnosis and assessment of prognosis of patients with NFLD.

TREATMENT

Modification of the lifestyle, Composed of food and exercise, foundation of NAFLD treatment and some tests have shown that it improves liver histology. Since insulin resistance is key to NAFLD's pathogenesis, therapies that address first of all we discuss obesity and insulin resistance followed by consideration of therapeutic lipid reduction, antioxidants, cytoprotective agents, tumor factor necrosis (TNF) substances and then new and emergence therapies.



WEIGHT LOSS THROUGH LIFESTYLE CHANGE

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The self-management diet program and minimal physical activity of obese or overweight patients with NAFLD should be prescribed. It has been shown that adherence to the combined dietary restriction and increased physical activity result in a greater and consistent weight loss that can be sustained over time. Several studies have looked at the impact of dietary weight loss accomplished with or without exercise. But several of these did not include a Control community and not histological information from paired liver biopsies before and after surgery. A small randomized controlled study of the impact of weight loss on NASH was conducted recently by Promrat and coworkers. They found a 12 months lifestyle treatment using a diet , exercise and behavior adaptation combination to effectively facilitate weight loss and improved steatosis and lobular inflammation without fibrosis. In pathogenesis and in the treatment of NAFLD, the nutritional structure also has a role. The diet was high in refined sugars and saturated fats and low in fibers and antioxidants in patients with hepatic steatosis.

Browning and collaborators and Westerbacka and colleagues have shown that lowering dietary intake of carbohydrates or fat content can be useful in lowering intrahepatic TG level. Zelber-Sagi and colleagues have recently shown that patients with NAFLD consume nearly double the amount of soft drinks compared to the general population, and their daily intake is associated with an increased risk to NAFLD regardless of age and gender, BMI and average daily calorie consumption. However, over the, most recent 2 years a number of studies have indicated that significant quantities of fructose as high-fructose corn syrup found in carbonated beverages can play an immediate job in the accumulation of liver fat. Specific dietary habits that also serve as unique goals for individual patients' behavioral changes, however a reasonable balance of diet should be achieved. While optima measure of activity to help long-term weight loss is unknown, weight reduction should be accomplished by striving for a calorie deficit of ~500 kcal / day (with combined dietary restriction and exercise), which should continue at a rate of ~0.5 kg per week. Small weight loss (8 per cent) was shown to enhance hepatic steatosis in patients with T2DM. The reduction of liver fat was accompanied by a dramatic improvement in the sensitivity of hepatic insulin, so that the suppression of insulin synthesis of hepatic glucose returned to normal. However, given that improvements in lifestyle associated with dietary restriction and exercise are so difficult for most patients to maintain, focus has shifted to other ways of achieving successful weight loss.

WEIGHT LOSS BY PHARMACOLOGICAL MEASURE

Patients who have failed to lose body weight through dietary modifications alone should be offered pharmacologic treatment for obesity. In several trials, an enteric lipase inhibitor, which diminishes dietary

fat ingestion, was assessed in NAFLD. In a pilot investigation of 10 hefty patients with NASH treated with orlistat for a half year, Harrison and partners exhibited a decrease in aminotransferase levels with improved liver histology in 9 out of the 10 patients. They noticed that changes in steatosis and fibrosis are usually linked to a 10 percent or more weight loss. In a small, double-blind, randomized , placebo-controlled study of patients with NAFLD, Zelber-sagi and coworkers, a double reduction in serum ALT level and a statistically significant reverse of the observed ultrasound of liver steatosis were shown to have taken place for 6 months. In a more recent open-label study, Hussein and his colleagues have had 14 patients receiving liver biopsy for six months or after diagnosis. At the end of the treatment period, 10 patients (70%) suffered a reduced fatty infiltration. Inflammation and fibrosis in 22 per cent changed by two grades and in 50 per cent by one grade. The Total cholesterol, TG, and low density lipoprotein cholesterol (LDL-C) serum aminotransferase level have been decreased, sensitivity to insulin has increased. The results included histological data from pairing liver biopsies, though the size of the cohort was restricted. Sibutramine is a reuptake agent for serotonin and norepinephrine, which functions by increasing satiety and helps reduce the consumption of food. Its use was compared or noted in obese patients with NASH.

Weight loss and improvements were observed in both serum aminotransferase and spectrum steatosis visible on ultrasound in both treatment classes, but histological results data were not available. Despite these promising results, concerns were raised about both these agents' long-term safety profile, and whether sustainable weight loss could be achieved. In up to 30 per cent of patients, Oder list causes gastrointestinal side effects and fat-soluble vitamins malabsorption, and sibutramine can increase blood pressure and heart rate. Indeed, the European Medicines Agency (EMA) has recently withdrawn sibutramine from use the medication has increased disease morbidity following an interim review of the Sibutramine Cardiovascular Outcome (SCOUT) trial. To sum up, there is extremely little popular evidence in clinical trials which supports the hypothesis that NAFLD will be improved in the short term by orlistat or sibutramine. No long-term information on the impact of these medicinal products on liver outcomes such as cirrhosis or its complications is currently available.

WEIGHT LOSS THROUGH BARIATIC THERAPY

Diet changes alone may not be sufficient to achieve sustained weight loss in patients with NAFLD who are extremely oesophisticated (BMI>40kg / m2) or who have BMI>35kg / m2, obesity-associated comorbidities; thus they may be considered a bariatric surgery. Restrictive gastric procedures (such as gastroplasty with vertical strips, adjustable gastric bands, and gastric bypass Roux-en-Y) minimize

gastric volume and create a mechanical barrier to feed intake. It encourages the reduction of weight and is actually the bariatric treatment of choice. At least 5 small studies investigated the impact of gastric bypass of Roux-en-Y on NASH.Paired liver biopsies in 108 patients before and after a gastric bypass of Roux-en-Y. All five studies reported various histological enhancements with up to 89 percent NASH resolution. The NAFLD results of gastroplasty were studied at least four trials. All four studies have shown an increase in hepatic steatosis but have mixed inflammation and fibrosis findings. Patients with laparoscopic adjustable gastric banding (LAGB) paired liver biopsies are minimally recorded. There have been two studies conducted on steatosis and fibrosis by the Dixon and colleagues following LAGB. There are evidence that a rapid loss of weight may lead to liver inflammation and development of fibrosis, although some authors remain concerned that the possibility of development of liver disease due to rapid weight loss within the first few months of postoperative surgery leaves the role of bariatric surgery in NAFLD care uncertain. However, the available evidence indicate that such procedures can be effective in setting sufficient surgical skills and can reverse both the NASH-related biochemical and histological defects.

INSULIN SENETIZING-AGENT

Biguanide metformin, either alones or with sulfo-nylureas or thiazolidinediones (TSDs), or insulins, is widely used globally to treat T2DM. Metformin's main anti-hyperglycaemic activity derives from an increased response to insulin, mainly in the liver and secondly in the skeletal muscle.

The key function of metformin within the liver is to minimize the development of hepatic glucose, mainly through gluconeogenesis inhibitors and also through glycogenolysis inhibitors. The rise in peripheral glucose ulitization (between 10 per cent and 30 per cent) is primarily due to nonoxidative glucose ulitization in the skeletal muscle. The most convincing evidence for the widespread use of metformin is from the massive United States. Diabetes prediction study with randomized placebo, metformin (850 mg twice daily) or lifestyle improvement program with 2.8-year follow-up compared to placebo in 3,234 glucose-reduced participants. Many research investigated the effects of metformin in NAFLD patients, showing a substantial increase in tolerance to insulin and serum liver enzymes with no weight gain but more complex improvements in hepatic histology. However, only two of these randomized trials were randomised.

Uygun and coworkers randomized 36 patients to calorie restriction alone or calorie restriction plus metformin.Significant improvement in serum aminotransferases and plasma insulin and C-peptide levels were noted in the metformin group. Although the metformin group observed greater improvement in

necroinflammatory function, the difference was not statistically relevant.

Bugianesi and colleagues randomized 55 patients to receive metformin 2000 mg daily for 12 months, 28 patients to receive vitamin E 800 IU / day and 27 patients to receive a prescriptive diet. Due to issues posed by the Ethics Committee, only 17 patients treated with metformin underwent biopsy at the end of treatment but substantial steatosis, necroinflammation and fibrosis decreases were recorded.

TZDs are a new class of medications that reduces the resistance of insulin directly by increasing insulin production in adipose muscle, adipose tissue and liver. The treatment of T2DM is currently approved for two TZDs, rosiglitazone and pioglitazone, as monotherapy or with other oral hypoglycaemic agents. TZDs function as agonists of the Gamma Receptor Proliferator (PPAR-B), which regulates multiple target genes with a nuclear liganda activated transcription factor. PPAR-ć is most commonly found in adipose tissues as well as in pancreas ß cells, endothelium vasculous, macrophages and skeletal muscle cells. TZDs improve the sensitivity of hepatic and peripheral insulin by allowing fatty acids to be absorbed into adiposal tissue, decreasing serum FFA rates, and increasing hepatic fatty acid oxidation. They also increase the development of insulin-sensitizing cytokine adiponctin and lower some pro-inflammatory mediators' circulatory levels. They will act as selective ligands of the PPAR-B receptors, primarily in adipose tissue. TZDs were shown to prevent progression to T2DM in high-risk individuals. Rosiglitazone is equal to placebo in the broadly randomized DREAM (Ramipril & Rosiglitazone Medications Prevention Assay), which significantly reduced the frequency of T2DM and increased the risk of a recurrence of Normoglycaemia in glucose-intolerant patients with no prior cardiovascular disease history. The above data form the basis of a NAFLD diagnosis for the clinical use of TZDs. Several pilot studies on the impact of TZDs on NAFLD and NASH showed promising results, both improving liver function tests and liver histology. In a big, recently published 12 month study for pioglitazone or daily diet and exert placebo Aithal and colleagues randomized 74 NASH biopsy-proven patients without diabetes. Follow-up biopsies were performed in 61 patients, which showed substantial improvements in liver damage and fibrosis in the pyoglitazone treated population after weight gains of about 3 kg. Ratziu and colleagues showed that rosiglitazone has significantly increased serum serum aminotransferase levels and steatosis histological score, although not necroinflammation or fibrosis, during the recent FLIRT (Fatty Liver Enhancement with Rosiglitazone Therapy) test. The research 'Pioglitazone or Vitamin E for Nonalcoholic Steatohepatitis,' which contrasts pioglitazone with vitamin E or placebo, is an significant and recently published major randomized, doubleblind, placebo-controlled trial. During 96 weeks 247 NAS HSN adults with no diabetes were randomly assigned to receive 30 mg / day (80 subjects), 800 IU / day of vitamin E (84 subjects), and placebo (83 subjects) for this study , conducted by NASH research network investigators for 96

weeks, Paired liver biopsies were pre- and post-treatment. The key result consisted of an improvement in the histological properties of NASH measured by a combination of standardized steatosis, lobular inflammation, hepatocellular ballooning and fibrosis. While the key test of pioglitazone was not positive for placebo, In addition to the increase in insulin resistance and the levels of liver enzymes, pioglitazone was associated with a significant decrease in steatosis, inflammation and hepatocellular ballooning. Thus, the pioglitazone subjects gained greater weight than the vitamin E or placebo subjects.TZDs tend to be comparatively more powerful than metformin. They need to be used constantly, however, as their advantages on discontinuation of treatment tend to be reversed.

Despite these beneficial findings, additional, adequately operated, randomized, placebo-controlled, longer -term in order to validate the histological benefit of the TZDs and NAFLD metformin, histological data trials from pair biopsies are needed. The side-effect profile of both medications should also be taken into account. Weight gain and congestive heart failure will result from TZD. Rosiglitazone also has deleterious effects on the density of bone minerals and can increase cardiovascular morbidity and mortality. The most serious gastrointestinal adversities [Scarpello and Howlett, 2008] are usually tolerated by metformin. Up until now, the US or European authorities did not consider metformin or TZDs for NAFLD treatment.

LIPID LOWERING-AGENT

Concern in the application of lipid reduction agents for diagnosis with NAFLD was based on the similarity of NAFLD to dyslipidaemia. Through competitively inhibiting hepatical reducctase coenzyme A (HMG CoA), statins reduce cholesterol production and thereby serum cholesterol output. These are commonly used to prevent more vascular events in patients with a vascular disorder and T2DM. The use of statins in patients with chronic liver disease posed concerns about their ability to induce hepatotoxicity. Statin use is now known to be relatively healthy, with recorded hepatotoxicity extremely rare in patients with compensated liver disease. Only several studies tested the effectiveness of the statins in NAFLD treatment. A very small pilot study was conducted by Rallidis and colleagues, investigating pravastatin use for 6 months in four NASH patients. In three patients, they reported improved inflammation and improved steatosis. Until now, only aminotransferases and steatosis have been shown to have a positive effect of atorvastatin. Despite the above, no conclusions on the efficacy of statins in NAFLD care can be drawn at present. There is some evidence that the NAFLD treatment can benefit from fibrates including clofibrate, fenofibrate and gemfibrozil. A 12-month pilot study comparing 16 biopsy-proven NASH patients treated with clofibrate and 24 NASH patients treated with ursodeoxycholic acid (UDCA) showed

substantial improvements in serum ALT and gamma glutamyl transpeptidase (GGT) levels and UDCA hepatic histology, but no significant changes in amino-transferase or hepatic histology in the clofibrate community.

A randomized 600 mg gemfibrozil randomized controlled 4-week trial showed significant changes to serum ALT levels but no histological information had been gathered. In the FIELD research, fenofibrate has been shown to decrease overall coronary events, primarily due to less non-fatal myocardial infarctions and revascularizations. In NAFLD patients, both liver enzyme and liver histology were shown to be increased by pioglitazone, a low-PPAR-a-activity TZD. Thus, fenofibrate may also be useful in NAFLD therapy, although this has yet to be tested in clinical trial.

The Ligands of PPAR-a are polyunsaturated fatty acids (PUFA). Deficiency of the long-chain multi-unsaturated acid (LCPUFA) n-3 sequence, with the resulting rise in the n-6 / n-3 fatty acid ratio contributes to PPAR-a role deficiency, together with hepatic absorption of FFA, hepatic ß-oxidation reductions and lipogenic transcription upregulation factor SREBP-1c. Studies in rats and mice have shown that n-3 PUFA enhanced diet improves insulin sensitivity, decreases liver TG and enhances steatohepatitis. An increased n-6/n-3 fatty acid ratio was detected in Araya and colleagues in comparison with control in patients with NAFLD. Capanni and colleagues reported a 12-month decreased level of serum ALT levels and hepatic steatosis echo-sound characteristics in 42 NAFLD patients with n-3 PUFA (1 g / day) during their first human pilot test. Zhu and colleagues have shown changes in serum ALT, fat content and standardization for ultrasonographic characteristics in a larger study of 144 NAFLD patients treated with n-3 PUFA (2 g / day) for 24 weeks. In both tests, the downside was that their ultrasound scoring systems were not clarified by hepatic histology.

ANTIOXIDANT

An interest in the therapeutic role of many antioxidants has been the hypothesis that NASH evolves in the treatment of NAFLD as a result of oxidative stress on the steatotic liver. a-tocopherol, the type of vitamin E primarily metabolized in humans, prevents B1 (TGF-B1) growth factor transformation that is supposed to result in fibrose production. Vitamin E impacts in NAFLD patients were examined by several pilot studies and three randomized controlled trials with contrary findings. For the first randomized , placebo-controlled trial, Harrison and colleagues randomized 45 patients who were diagnosed with biopsy-proven NASH to 6 months with vitamin E (1000 IU / day) plus vitamin C (1000 mg / day). Repeated liver biopsy revealed a minor increase in vitamin E fibrosis but no substantial change in inflammation or necrosis. In a second controlled trial, 16 adults were randomized to vitamin E (800 IU /

day) with biopsy-proven NASH and diet and exercise versus diet and training alone for 12 weeks. Both patients displayed elevated aminotransferases in weight and serum, but the authors found a no longer purely lifestyle-changing benefit of vitamin E. Recently released PIVENS studies indicate that vitamin E was correlated by using a combination of standardized values for steatohepatitis, lobular inflammation, hepatocyte ballooning, and fibroidism with substantially higher rate changes in NASH's histological characteristics relative to placebo. Vitamin E was related to decreased hepatic steatosis and lobular inflammation, but not to improved fibrosis rates. Betaine (trimethylglycine) is a naturally occurring choline metabolite that serves as an alternative methyl donor in the conversion of homocysteine to methionine and in the production of phosphatidylcholine from phosphatidylethanolamine. Phosphatidylethanolamine is an alternative methyl donor. Phosphatidylcholine (lecithin) and VLDL cell membranes represent the mechanism through which TG is exported from the liver. Betaine has theoretical advantages of S-adenosyl-methionine (SAMe) antioxidants (phosphatidylcholine synthesis) and cell membrane stabilization. Although the serum aminotransferase levels of the seven study participants were statistically significantly improved, the amount of steatosis, histological inflammation and fibrosis did not increase statistically significantly. Longer regulated betaine studies need to be performed before any recommendations on its use in NASH can be made. Checked in animal hepatic models were N-acetylcysteine. Gulbahar and colleagues note modifications to amino-tranferases, although no liver biopsies were performed in a small human sample of 11 NASH-administered dietary regulation, followed by N-acetylcysteine therapy. Many researchers have suggested that intestinal flora endotoxins can also contribute to oxidative stress in the liver. The modification of this flora with the probiotic has been demonstrated in the NAFLD animal models to minimize oxidative and inflammatory liver damage Loguercio and his colleagues tested the same agent in 22 patients with NAFLD and showed a strong tolerance. They reported positive effects on aminotransferases and markers of the lipid peroxidation, but there were no biopsies. Increased triacylglycerol hepatic intakes in rats are oligofructose, an indigestible fructane. In an 8-week, double-blind crossover study, Daubioul and his colleagues randomized seven NASH patients for oligofructose or placebo. Following 4 weeks of therapy insulin levels increased and after 8 weeks aminotransferases increased. The role of iron in pathophysiology of the NAFLD is uncertain, but it can lead in the development of disease, as high levels of hepatic iron are a source of insulin resistance and are associated with oxidative stress. Pholebotomy in this regard has been tested in non-randomization studies to achieve 'near iron deficiency' and has demonstrated improvement in serum aminotransferase and insulin power. However, in major randomized controlled studies, this intervention also requires histological validation.

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Recent advance in treatment of Non Alcoholic fatty liver Disease

CYTOPROTECTIVE AGENT

UDCA is a bile acid that is found in humans in limited amounts of hydrophilic dihydroxide. This is believed to function by competing in the bile acid reservoir for displacing hepatotoxic endogenous endogenous bile acids and has a cytoprotective effect via the stabilisation of cell membranes and inhibition of apoptosis. Nonetheless, these findings were not replicated in a massive, multicenter, randomized placebo-controlled study performed by Lindor and colleagues. One hundred and sixty-six patients with biopsy-proven NASH were randomized to receive either UDCA (13–15 mg / kg / day) or placebo for 2 years. The trial was completed by one hundred and 216 patients and 107 patients received post-treatment biopsies. Since the study, only the treatment group and the placebo group have demonstrated changes in transaminases and steatosis with no difference between the two groups. The authors concluded that the improvement of liver enzymes or histology in UDCA as a single agent and at a given dose was not correlated with placebo. However, Durfour and colleagues have documented improved biochemistry and histology, particularly due to regression of hepatic steatosis, in biopsy-proven NASH patients treated with UDCA and vitamin E against UDCA alone and placebo. UDCA's favorable safety profile and its proven efficacy in other types of liver disease indicate further analysis of its possible function in NASH treatment, either at higher doses or with other agents in combination. Lecithin, which has antioxidant and cytoprotective activity, raises plasma-free levels of choline and reduces hepatic steatosis in long-term patients with total parenteral nutrition. Future pilot studies should be considered with this tool.

ANTI TNF-AGENTS

A derivative of xanthine that decreases blood viscosity, pentoxifylline has become more worrying because of its capability of nonspecifically suppressing TNF-a. In patients with NASH, the safety and efficacy of two small open-label studies. Adams and coworkers and Satapathy and colleagues both reported reduced aminotransferases after 12 months of pentoxifylline therapy open label. N further research, Satapathy and colleagues treat nine patients for 12 months with pentoxifyllin-proven NASH biopsy and showed a reduction in steatosis, lobular inflammation and fibrosis in the liver biopsy follow-up process. Improvements in aminotransferases mirrored certain histological changes. This will be beneficial to further explore such preliminary results in larger, randomized controlled trials.

LIVER TRANSPLANTATION

Where cirrhosis occurs complicated with hepatocellular carcinoma and end stage liver failure, liver transplantation may be necessary. While this number excludes patients with cryptogenic cirrhosis, ~3

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per cent of in reality, all transplants are done for the NAFLD end-stage in North America. The recurrence of steatosis after transplant is normal with steatohepatitis progression reported in a third of cases.

NEW AND EMERGING THERAPIES

The essential hypertension and insulin resistance are very much associated with insulin resistant about half of all patients with essential hypertension. In regulating blood pressure the renin-angiotensin system (RAS) plays a major part and plays a major role in the resistance to insulin. RAS suppression increases intracellular insular signaling by activating PPAR-μ and prevents hepatic stellate cell activation, which decreases the possibility of hepatic inflammation and fibrogenesis. Yokohama and colleagues were diagnosed with an angiotensin receptor blocker (ARB) at 50 mg / day for seven NSH patients and 48 weeks of loartan hypertension.Five patients received follow-up biopsies with reduced necroinflammation and four patients with reduced fibrosis. Enjoji and coworkers recently reported an improvement in the sensitivity to hepatic insulin (HOMA-IR) and ALT levels of telmisartan and olmesartan in NAFLD patients. In the case of patients with NAFLD, randomised controlled studies should be examined considering the common usage of Angiotensin receptor blockers to treat hypertension. Analogs such as exenatide and liraglutide have been found to facilitate insulin secretion and inhibit glucagon secretion, gastronic emptying and satiety in conjunction with mild weight loss in patients with T2DM Glucagon-like peptide-1 (GLP-1). In animal models the GLP-1 agonist exen-4 reduced resistance to insulin, oxidative stress marks and liver steatosis, suggesting that erratic therapies may be a novel therapeutic alternative for human NAFLD. The short acting repaglinide and nateglinide insulin secretagogs have also been seen as possible NAFLD therapy options. Morita and colleagues randomized 10 patients with T2DM and biopsy confirmed NASH with food , exercise and diet and exercise for 20 weeks alone to receive 270 mg / day of nateglinide. Postprandial glucose recovery, glycosylated hemoglobin, tests of liver function, in the nateglinide culture, imagery and histological observations of NAFLD were noted.

SUGGEST TREATMENT ALGORITHM FOR PATIENTS WITH NAFLD

The effectiveness and protection of pharmacotherapy in NAFLD treatment remains unfinished, after almost two decades of research and clinical trials. Many of the studies performed had methodological weaknesses, such as the lack of randomization, limited sample size, short follow-up time and lack of histological data on paired liver biopsies, which make it hard to draw final conclusions. Actually there is no single drug agent approved to treat NAFLD. Thus, a holistic approach will be used for NAFLD emergency care practitioners, tailoring treatment to suit individual needs. A suggested treatment algorithm is shown infigure

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Recent advance in treatment of Non Alcoholic fatty liver Disease

A lifestyle change is the cornerstone of all patients with the condition, including healthy eating, daily physical activity and reduced alcohol consumption by less than 14 units per week with alcohol for at least 1-2 day off. Both patients should be required to take part in clinical studies. For NAFLD patients who are overweight or obese through lifestyle changes, in the first case, weight loss should be promoted. If the patient fails and has a MIC > 28 kg / m2, orlistat may be tested for pharmacological therapy. Bariatric surgical referral should be considered for patients with BMI > 40 kg / m2 (35 kg / m2 if they are also comorbid, such as hypertension or T2DM). In order to increase the burden of cardiovasculatory disease with significant morbidity and mortality in NAFLD, care is required pharmacologically to monitor cardiovascular risk factors (such as hypertension and dyslipidemia). More than one antihypertensive agent might be necessary to achieve a blood pressure target of less than 140/90 mmHg and ARBs are required , particularly for T2DM patients with renoprotective effects. Statins and fibrates are now also

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recognized as safe in NAFLD patients and are available for the prevention of primary cardiovascular diseases in the high-risk hypercholesterolemia and hypertriglyceridemia patients, and Hyperglycaemia and computer-supplemented metformin should be handled strongly with dietary and behavioral modification in the first line in patients who already receive T2DM. Alone in these steps, TADs, sulphonylurea or untruthin-based therapy should be applied instead of achieving target glycosylated hemoglobin (HbA1c) ranging from 6.5 to 7.0 percent. The advantage of incretin-based therapy with TZD and sulphonylurea is that there is no more weight growth, and only weight loss or weight loss is in many cases supported.

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