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RESEARCH ARTICLE

FATTY LIVER

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) includes a broad spectrum of alterations that go from simple steatosis to steatohepatitis and cirrhosis. Type 2 diabetes mellitus (DM-2) and obesity are the principle factors associated to NAFLD. A 20-30 % prevalence in general population has been described. The survival of this type of patient is lower than the general population's, showing a higher incidence of hepatic and cardiovascular complications. The aetiopathogenesis is still unclear, but we know the intervention of different factors that produce fatty-acid accumulation in hepatic parenchyma, causing oxidative stress, oxygen-free radicals and the synthesis of an inflammatory cascade, that determine the progression of this disease from steatosis up to advanced fibrosis. The diagnostic gold-standard is still the liver biopsy, even though the development of newer non-invasive techniques, like serological and imaging (radiology), have opened a new field for research that allows bloodless testing of these patients and better study of the natural history of this disease. Nowadays, there is still no specific treatment for NAFLD. The development of healthy life habits and moderate exercise continue to be the pillars of treatment. Different pharmacological approaches have been studied and applied, such as the control of insulin resistance, lowering cholesterol levels, antioxidants, and other alternatives in experimental trials.

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INTRODUCTION

The non-alcoholic fatty liver disease (NAFLD) can develop a wide variety of clinical and pathological manifestations that are undistinguishable from those observed in alcoholic patients [(1)] . The NAFLD is secondary to the fat accumulation, especially in the form of triglycerides in the hepatocytes and these patients may show simple hepatic steatosis lesions, steatosis with inflammation (non-alcoholic steatohepatitis, NASH), cirrhosis and hepatocellular carcinoma (HCC) [(2)]. Diabetes mellitus type 2 (DM-2) and obesity are the principal factors associated with NAFLD, which is considered the hepatic manifestation of the metabolic syndrome, and its prevalence increases in parallel with these two diseases. It is estimated that NAFLD is the first cause of chronic elevation of liver function texts in the USA and it is believed that cryptogenic cirrhosis may be associated with it [(3)].

Epidemiology: The prevalence of NAFLD in western countries is 20-30 % and about 15 % in Asian countries. It has been observed in all age groups, including children, where the prevalence is 10-15 % (less than in adults). As a general rule, the prevalence increases with age, affecting equally both sexes [(3)]. Between 90-100 % of the patients diagnosed with obesity present some degree of NAFLD. Amongst those who have DM-2, the prevalence is around 10-75 % and in those with hyperlipidemia it is between 20-35 %, and in patients with cirrhosis around 3 % [(1,4)]. NAFLD may be the most frequent cause of persistent hypertransaminasemia and cryptogenic cirrhosis in adults [(5)]. The variability of manifestations, of progression and the natural course of this disease amongst individuals of different race, and the incidence observed in some families, has awakened the interest in the studies of genetic mutations that could determine a genetic predisposition. For now the genes responsible for this remain unknown, but several candidates have been proposed: a) genes related to abdominal obesity and DM-2; b) genes that suppress the exit of very low-density lipoprotein (VLDL) from the hepatocytes; c) mutations and polymorphism of genes associated with oxidative stress or of the protecting enzyme superoxide dismutase; and d) genes responsible of inflammatory response and fibrogenesis [(6)]. Among these mutations under study we find the over-expression of genes like TNF-a, M-CSF (macrophage colony stimulating factor) and TRAIL-R2 (apoptosis mediated receptor)[(7)].

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The existence of a nonsynonymous polymorphism for rs738409 in the gene PNPLA3 [8] predicts the future outcome of patients with NAFLD and its association with fibrosis. Today's studies are focused on "genome-side association" type analysis in order to identify markers for the severity of NAFLD [6].

Natural History: The progression of this liver condition depends on the level of histological damage at the time of diagnosis, meaning that fatty liver disease (FLD) tends to remain more or less stable while non-alcoholic fatty liver disease (NAFLD) tends to lead to cirrhosis and hepatocellular carcinoma (HCC). The gold standard diagnosis is liver biopsy, but with this long-duration liver disease it is difficult to follow large groups of people by means of serial biopsies; in an attempt to avoid this invasive method the diagnostic and prognostic implementation of different non-invasive methods has been studied [9].

In a developmental study of 132 patients during a 10-year follow-up period it was revealed that 25 % of patients with NAFLD had progressed to cirrhosis – 12 % died due to liver disease [7]. The factors that imply a greater risk of progression of NAFLD are: Age over 40 years, body mass index (BMI) > 40 kg/m^2, an AST (aspartate aminotransferase)/ALT (alanine aminotransferase) ratio greater than 1 and the coexistence of DM-2 or hyperlipidemia. Mortality associated with NAFLD depends on the stage of the disease, since patients with FLD or minimal fibrosis have a very low risk of death after 10 years. However, those with more advanced lesions are at risk of suffering complications such as hepatocellular failure, bleeding varices, ascites, hepatorenal syndrome and HCC. The risk of mortality is higher than in patients with cirrhosis from other causes, due to the association of NAFLD with metabolic factors and cardiovascular risk [3,10]. A histological improvement in some patients with NAFLD has also been described [9]. After losing weight, a decrease in inflammation and even perisinusoidal fibrosis is detected, especially if weight loss is gradual and diet is associated with physical exercise [11]. In some cases, liver failure occurs due to rapid weight loss, regardless of the cause, but especially in morbidly obese patients undergoing bariatric surgery [3,10].

Causes: Fatty liver (FL) is commonly associated with metabolic syndrome (diabetes, hypertension, obesity, and dyslipidemia), but can also be due to any one of many causes:[12][13]

Alcohol: Alcoholism is one of the causes of fatty liver due to production of toxic metabolites like aldehydes during metabolism of alcohol in the liver. This phenomenon most commonly occurs with chronic alcoholism.

Metabolic: Abetalipoproteinemia, glycogen storage diseases, Weber–Christian disease, acute fatty liver of pregnancy, lipodystrophy.

Nutritional: Obesity, malnutrition, total parenteral nutrition, severe weight loss, refeeding syndrome, jejunoileal bypass, gastric bypass, jejunal diverticulosis with bacterial overgrowth.

Drugs and toxins: Amiodarone, methotrexate, diltiazem, expired tetracycline, highly active antiretroviral therapy, glucocorticoids, tamoxifen,[14] environmental hepatotoxins (e.g., phosphorus, mushroom poisoning).

Other: Celiac Disease,[15]inflammatory bowel disease, HIV, hepatitis C (especially genotype 3), and alpha 1-antitrypsin deficiency[16].

Risk Factors: Known risk factors for development of NAFLD are overeating of sugar, fructose and fat. Foods containing high sugar and fructose that include desserts, sweetened drinks and carbonated drinks. Many processed foods contain transfat, butter and margarine. For example, cake, cookie, donut, potato chip and bakery. Additionally, consumption of fatty meats, pork and beef, promote accumulation of abdominal fat, visceral fat and ectopic fat. These unhealthy dietary patterns result in overweight, obesity, and insulin resistance [17,18]. It also shares risk factors with diabetes, metabolic syndrome and cardiovascular diseases.

Pathogenesis: NAFLD is considered as a metabolic disorder that results from complex interaction between genetic, hormonal and nutritional factors.[19]Recent evidence suggests that several genetic risk factors predispose to the development and progression of NAFLD.[20]For example, polymorphisms of PNPLA3, TM6SF2, FTO, LIPA, IFNl4 HFE, and HMOX-1 genes have been found to be associated with development/progression of the disease. Obesity and metabolic syndrome (MS) are the most important risk factors identified in the development of NAFLD, and diabetes mellitus and hypertension are also linked to greater progression of the disease.[21,22]Because of the similarity in pathogenesis –IR leading to hyperinsulinemia and gross alterations in carbohydrate and fat metabolism – NAFLD and T2DM often co-exist in many individuals with metabolic syndrome. Moreover, both the disorders modify the risk for each other in a vicious circle.[23]Full-blown T2DM also contributes to further worsening of hepatic steatosis and progression of established NASH, fibrosis and cirrhosis, with a higher risk of development of HCC.[22,23]

Hyperinsulinemia and IR lead to increased adipocyte lipolysis and circulating free fatty acids (FFAs) that are taken up by hepatocytes, initiating various complex metabolic pathways that lead to NAFLD (Fig. 1).[24]Because of the very strong association with MS, NAFLD is considered as the hepatic component of MS.[22,24]Systemic IR reduces plasma adiponectin (an adipokine that increases insulin sensitivity and reduces inflammation) levels and increases the concentration of leptin (a cytokine secreted by adipocytes that plays a role in reducing body weight and fat mass). Reduced adiponectin levels[25]and increased leptin levels (possibly from leptin resistance)[26]are observed in patients with NAFLD.[24] Adipose tissue lipolysis continues, even with hyperinsulinemia, because of the IR that results in increased plasma FFA concentration. Liver takes up the FFA in circulation, that if not oxidised gets stored in the liver in various forms or exported as very low density lipoproteins (VLDLs), as shown in the figure. High hepatic VLDL output also results in high circulating triglycerides and LDL and low circulating high density lipoprotein (HDL) levels that increase atherosclerosis risk.[27] Increased glucagon levels with altered insulin/glucagon ratio is seen in patients with NAFLD.[24]This promotes hepatic de novo lipogenesis (DNL), glycogenolysis and gluconeogenesis with higher hepatic glucose production and IR. Several gastrointestinal hormones and adipokines that regulate glucose

and lipid metabolism, along with hormones controlling appetite and satiety, are also thought to contribute to the pathogenesis of NAFLD.[19,22,24]Glucagon-like insulinotropic peptide-1 (GLP-1), ghrelin, selenoprotein P, leptin, adiponectin and the myokine – irisin – are some of these chemicals.[24]As in the case of T2DM, the predominant risk factor for development of NAFLD is IR because of overweight/obesity that result from adverse lifestyle factors, such as overnutrition and physical inactivity. Although the majority of cases with NAFLD are obese/overweight individuals, a small but significant proportion of patients with the disease are lean. This phenomenon is especially common in the non-Caucasian populations, accounting for about 20% of cases.[28]

Predominant visceral obesity rather than generalized obesity, high dietary intake of fructose and cholesterol, and genetic risk factors may predispose to non-obese NAFLD.[29]Higher rates of the mutant PNPLA3 gene variants and reduced serum adiponectin concentrations were reported in Caucasians with lean NAFLD compared to controls in a recent report.[30]Potential roles of various lysophosphatidylcholines, phosphatidylcholines, lysine, tyrosine and valine were revealed in these cases using metabolomics studies. Physical activity stimulates production of various soluble chemicals from muscle fibers, collectively termed as myokines, that show auto, para and endocrine functions.[31,32]These myokines function as messengers between skeletal muscle and other tissues, such as liver, adipose tissue, heart, brain and blood vessels, signaling cascades of neurohormonal changes that modulate energy balance, metabolism and homeostasis. Although several myokines are described that may alter human metabolism, irisin is the most studied one among them. Physical activity increases irisin levels, leading to thermogenesis with a possible protective effect on metabolic disorders.[33]However, there are studies showing increased levels of irisin in patients with metabolic syndrome and NAFLD.[34,35]

Acute response to exercise is shown to involve an increase in plasma irisin levels, whereas chronic exercise leads to reduction of the levels.[36]Therefore, these conflicting reports on the plasma levels and metabolic effects of irisin may be related to development of resistance to the hormone or its effectors at tissue level that should be elucidated in future research. With the available evidence, we can conclude that by modulation of multiple metabolic parameters and the effects on body energy homeostasis, irisin may alter the risks for obesity, T2DM, NAFLD and cardiovascular disease.[32,37] Alterations in the functions and composition of gut microbiome, otherwise known as intestinal dysbiosis, have been found to associated with obesity and its consequent metabolic disorders, including NAFLD, in animal models.[38]Several subsequent studies in animal models and humans revealed clear association between gut dysbiosis and NAFLD.[39]Even the degree of intestinal dysbiosis has been found to be correlated to the severity of NAFLD and the fibrosis.[40]Several local and systemic factors, such as disruption of gastrointestinal mechanical barrier function,[41]inflammation,[42]various metabolites released by intestinal microbial metabolism/ actions,[43,44]and ethanol production by the microbiota [45]were proposed as the potential pathogenic mechanisms.

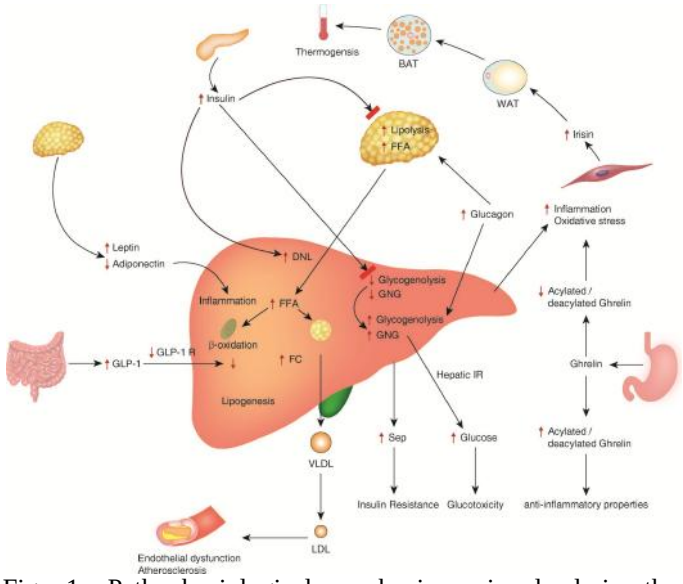

Fig. 1. Pathophysiological mechanisms involved in the development and complications of nonalcoholic fatty liver disease (NAFLD). BAT, brown adipose tissue; DNL, de novo lipogenesis; FC, free cholesterol; FFA, free fatty acid; GLP-1, glucagon-like insulinotropic peptide; GNG, gluconeogenesis; IR, insulin resistance; LDL, low density lipoprotein; SeP, selenoprotein P; VLDL, very low density lipoprotein; WAT, white adipose tissue. Figure reproduced with permission from Pettaet al.[24]

Signs and Symptoms: Often there are no or few symptoms.[46] Occasionally there may be tiredness or pain in the upper right side of the abdomen.[46]

Diagnosis: NAFLD remains asymptomatic in a significant proportion of patients, and the diagnosis is often suspected when liver functions are found abnormal on biochemical testing or hepatic imaging (ultrasonography, computed tomography [CT] or magnetic resonance imaging [MRI] of liver) suggestfatty liver, when performed for some other reasons. The diagnosis of NAFLD is established when $ 5% of the hepatocytes show steatosis in the absence of causes for secondary steatosis, such as excessive alcohol consumption (> 20 grams/day in females and 30 grams/day in males) or chronic liver conditions associated with steatosis (viral, autoimmune, metabolic and toxic disorders).[19,47,48]

Biochemical markers: Liver enzymes can often be normal in a number of patients with NAFLD. For example, alanine aminotransferase (ALT) can be normal in up to 60% of patients with NASH, and 53% of patients with high ALT had no evidence of NASH and advanced fibrosis.[49,50]Although several biochemical markers, such as TNF-a, IL-6, CRP, Pantraxin, Ferritin, serum prolidase enzyme activity, soluble receptor for advanced glycation end product and cytokeratin-18, have been proposed as useful in predicting the severity of NAFLD/NASH in the past, none of these markers have shown sufficient sensitivity or specificity for routine clinical application for diagnosis.[51] NAFLD fibrosis score (NFS) using clinical and biochemical parameters to predict the severity of liver involvement is the most validated non-invasive tool to assess the disease. NFS is based on age, body mass index, aspartate transaminase (AST), ALT, platelets, albumin, and presence or absence of impaired fasting glucose.[19]A low cut-off score < 1.455 excludes advanced fibrosis with a negative predictive value of 93%, while a high

cut-off value exceeding 0.676 suggests advanced fibrosis with a positive predictive value of 90%.[19,52] Although the specificity of NFS is good, the sensitivity was recently reported as being low.[53]

Radiological Diagnosis

Ultrasonography, CT and MRI of the liver are the standard imaging modalities used in clinical practice for diagnosis of NAFLD. In general, about 30% of liver steatosis should be present for these techniques to detect NAFLD.[19,22,47] Ultrasonography is cheap, available easily and easy to perform, even from the bedside. The reported sensitivity of the test is > 90 % in experienced hands when hepatic steatosis is >30 %, although the sensitivity is much lower at lower degrees of steatosis.[54,55] However, ultrasonography is highly operatordependent and, therefore, results can vary widely depending on the performer.

Transient elastography (TE) is an ultrasound-based imaging technique to detect the degree of fibrosis in patients with NAFLD and NASH. Sensitivity and specificity of TE to diagnose various stages of fibrosis have been reported to be 79–92% and 75–92% respectively.[56] Recent evidence also suggests that ultrasound-based controlled attenuation parameter value used in the TE technique can predict the degree of steatosis in patients with NAFLD.[57] CTscan is reported to be highly sensitive in quantifying the hepatic and visceral fat to measure the degree of adiposity in patients with metabolic syndrome and NAFLD.[58] However, the test is expensive and associated with risk of radiation, and, therefore, not usually recommended in clinical settings. MRI is highly sensitive and specific for both quantitative and qualitative assessment of NAFLD. Newer MRI techniques, such as MR elastography, proton density fat fraction and the FerriScan method, can stage the degree of fibrosis non-invasively to diagnose and assess the prognosis of patients with NAFLD.[58] However, these techniques are expensive and available only in specialized centers.

Diagnosis at US: The echogenicity of the normal liver equals or minimally exceeds that of the renal cortex or spleen. Intrahepatic vessels are sharply demarcated, and posterior aspects of the liver are well depicted. Fatty liver may be diagnosed if liver echogenicity exceeds that of renal cortex and spleen and there is attenuation of the ultrasound wave, loss of definition of the diaphragm, and poor delineation of the intrahepatic architecture [59,60]. To avoid false-positive interpretations, fatty liver should not be considered present if only one or two of these criteria are fulfilled.

Diagnosis at CT: At unenhanced CT, the normal liver has slightly greater attenuation than the spleen and blood, and intrahepatic vessels are visible as relatively hypoattenuated structures. Fatty liver can be diagnosed if the attenuation of the liver is at least 10 HU less than that of the spleen [59,61,62] or if the attenuation of the liver is less than 40 HU[63,64]. In severe cases of fatty liver, intrahepatic vessels may appear hyperattenuated relative to the fat-containing liver tissue [59]. Other CT criteria have been advocated. Ricci et al, for example, measured the liver to spleen attenuation ratio and interpreted a ratio of less than 1 as indicative of fatty liver [65].This group also quantified liver fat by performing unenhanced CT in conjunction with dedicated fat calibration phantoms. At contrast material-enhanced CT, the comparison of liver and spleen attenuation values is not as reliable for the diagnosis of fatty liver, because differences between the appearance of the liver and that of the spleen depend on timing and technique and because there is overlap between normal and abnormal attenuation value ranges [66,67].Fatty liver can be diagnosed at contrast-enhanced CT if absolute attenuation is less than 40 HU, but this threshold has limited sensitivity.

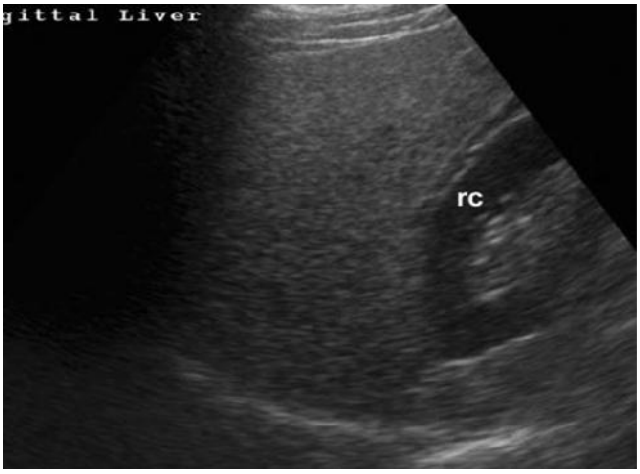

Figure 1. Diffuse fat accumulation in the liver at US

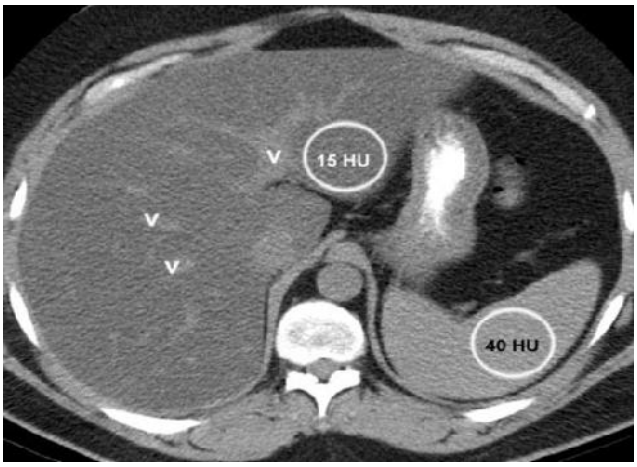

Figure 2. Diffuse fat accumulation in the liver at unenhanced CT

Diagnosis at MR imaging: Chemical shift gradient-echo (GRE) imaging with in-phase and opposed-phase acquisitions is the most widely used MR imaging technique for the assessment of fatty liver.The signal intensity of the normal liver parenchyma is similar on in-phase and opposed-phase images.Fatty liver may be present if there is a signal intensity loss on opposed-phase images in comparison with in-phase images [68,69], and the amount of hepatic fat present can be quantified by assessing the degree of signal intensity loss [70]. Fat deposition also can be diagnosed by observing the signal intensity loss of liver on MR images after the application of chemical fat saturation sequences, but this method is less sensitive than is chemical shift GRE imaging for the detection of fatty liver.

Liver biopsy and histology: Liver biopsy remains the gold standard for diagnostic evaluation of NAFLD. Biopsy not only confirms the diagnosis but provides information on extent of fibrosis and steatosis, necro-inflammation, and architectural distortion.

In the past, the NASH Clinical Research Network histological scoring system was the widely used histological scoring system, representing a validated scoring system that generates a NAFLD activity score (NAS). A NAS score of 5 or > 5 is considered NASH and < 3 is not NASH.[71] However, recent evidence suggests that NAS score cannot be used as a surrogate for discrimination between NASH and NAFLD, although it is useful for the histological diagnosis.[72,73] Therefore, the European Association for the Study of liver recommends NAS for evaluation of the disease activity, and not for the diagnosis. The steatosis, inflammatory activity and fibrosis (SAF) score introduced in 2012, provides a reliable and reproducible measure for the diagnosis, grading and staging of NAFLD without much inter-observer variability.[74]SAF score assesses both and separately the grade of steatosis (S), the grade of activity (A), and the stage of fibrosis (F), the latter according to the NASH Clinical Research Network. Cost, procedure-related complications and intra- and inter-observer variations in reporting the histology are the major draw backs of liver biopsy, and, therefore, it is usually not recommended in clinical practice, except in circumstances where other differential diagnoses are to be excluded.

Treatment: There is no single intervention that is proven to be fully effective in the treatment and cure of NAFLD. The main goals of treatment are to improve steatosis and to prevent progression of the disease. Intense lifestyle modification and treatment of the risk factors are the cornerstones of disease management. Medical and surgical interventions serve as second-line treatments, or as adjuvants.

Lifestyle interventions: Sustained and effective weight loss through calorie restriction and increased physical activity have been shown to improve liver function and histology in multiple studies. [75,76]Both exercise and dietary interventions in isolation or in combination have been shown to improve biochemical and histological parameters of NAFLD. Low-carbohydrate high-fat diet has been shown to be effective in improving all the abnormal clinical and biochemical parameters of metabolic syndrome and NAFLD in multiple studies.[77]These dietary interventions are also associated with weight loss in patients. Even without significant weight loss, however, lifestyle interventions were found to improve NAFLD, especially if patients are adherent to the changes.[78]Yet, patient compliance issues always represent a challenge to these interventions.

Insulin sensitizing agents: Being a disease associated with IR and metabolic syndrome, insulin sensitizing agents are expected to alter the pathophysiological mechanisms of NAFLD. Metformin and the thiazolidinedione group of antidiabetic agents are the most studied medications in this group.

Metformin: Although metformin use was associated with significant improvements in IR and liver transaminases (AST and ALT), the drug failed to show improvement in the histological parameters, such as steatosis, inflammation, hepatocellular ballooning and fibrosis.[79]However, because of the antidiabetic efficacy, metformin should be considered for patients with T2DM or even prediabetic states and NAFLD. Metformin is found to be safe, even in patients with cirrhosis, and may protect against development of HCC in cases with T2DM and chronic liver diseases.[80]

Thiazolidinediones: These drugs modulate tissue insulin sensitivity through the peroxisome proliferator activated receptor (PPAR)-g signaling, and improve blood glucose control. Rosiglitazone and pioglitazone are the agents widely studied in this class of drugs for management of T2DM. Following the controversy about increased cardiovascular events, rosiglitazone use has been much lower in recent years, with pioglitazone being the agent widely used currently. Pioglitazone has been shown to improve the hepatic insulin sensitivity and fatty acid oxidation, and to inhibit hepatic lipogenesis.[81]There is moderate quality evidence to suggest the benefits of pioglitazone in improvement of biochemical and histological parameters of NAFLD, although the drug use may be associated with weight gain.[82,83]In combination with intense lifestyle modification, this drug should be considered in patients with NASH.

Antioxidants: Oxidative stress plays a major role in the pathogenesis of NAFLD and several investigators studied the effects of antioxidants extensively.[82–84]Vitamin E is the most studied antioxidant in this group. Supplementation of this was associated with significant improvement in all histological parameters, such as steatosis, hepatocyte ballooning, lobular inflammation and fibrosis, as compared to placebo.[85]Vitamin E is used in the dose of 800 International Units daily for patients with NASH, especially in non-diabetic cases.[19,84]Although multiple agents such as N-acetylcysteine, betaine, probucol, viusid, and silibinin (milk thistle) have been used in different trials, the use of these agents are not recommended in current clinical practice because of conflicting/insufficient evidence on the benefits.[84]

Incretin-based therapy: There are two main groups of incretin-related drugs extensively studied for use in NAFLD, viz., GLP-1 analogues (e.g., exenatide, liraglutide, lixisenatide, dulaglutide and semaglutide) and dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g., sitagliptin, saxagliptin, vildagliptin, alogliptin and linagliptin). Both classes of drugs augment the meal-related insulin secretion from the pancreas, along with extra-pancreatic effects on multiple organs that make them very useful for the management of T2DM.[86]Use of GLP-1 analogues are associated with weight loss, and DPP-4 inhibitors are weight neutral. Incretin-based therapy is very commonly used in overweight/ obese T2DM patients, many of whom suffer from NAFLD as well. Remarkable benefits of both the conditions make this class of agents unique in managing the cases.[22] Recent evidence suggests that patients with NASH, particularly those with T2DM, get significant benefits from GLP-1 analogue therapy, with improvement in liver histology and reduction in liver transaminase levels from baseline.[87,88]In patients with NAFLD/NASH with or without T2DM, the benefits of GLP-1 analogue therapy may outweigh the risk of use, and, therefore, it should be considered. Although less effective, DPP-4 inhibitors are also reported as effective in patients with NAFLD and T2DM.[22,89]

Lipid lowering agents: Lipid lowering agents are useful for treatment, especially in patients with concurrent dyslipidemia and NAFLD. A Cochrane review in 2013 reported possible improvements in serum aminotransferase levels and ultrasonological abnormalities in cases treated with statins, although the studies included in the review were small with high risk of bias.[90]The review concluded that statins can improve the adverse outcomes related to NASH in patients with concurrent diseases, such as hyperlipidemia, diabetes mellitus, and metabolic syndrome.

A more recent small randomized control trial (RCT) found that rosuvastatin monotherapy could ameliorate biopsy-proven NASH with resolution of metabolic syndrome within 12 months of treatment.[91] Unfortunately, the potential for complications associated with liver biopsy makes it difficult to perform large RCTs in patients with NASH. In experimental models of NAFLD, fenofibrate use was also found to reduce liver steatosis associated with high-fat diet, T2DM and metabolic syndrome.[92] Some small clinical studies also showed beneficial effects. However, small sample sizes and lack of histological data limit the validity of these results.[92] Multiple RCTs and meta-analyses showed beneficial effects of omega-3 fatty acids both in adults and children with NAFLD.[93,94] Propr otein convertase subtilisin/kexin type 9 (PCSK9) is a molecule secreted by hepatocytes that inhibits uptake of LDL by targeting the receptor for degradation, and which augments lipogenesis.[95] Circulating PCSK9 levels have been found to be elevated in patients with NAFLD. PCSK9 inhibitors have been recently shown to be highly effective in reducing hypercholesterolemia in patients with remarkable improvement of the associated cardiovascular risk.[96] Because the treatment is expensive, these drugs are often reserved for patients with statin intolerance and familial forms of lipid disorders inadequately managed by full doses of other lipid lowering agents.

Drugs for weight loss: Medications that help weight loss may potentially alter the pathogenic mechanisms of NAFLD and may be useful in selected patients. Most of these medications are associated with only modest weight loss benefit and several of them have been withdrawn from the market owing to undesirable side effects.

Orlistat: This medication inhibits pancreatic lipase, resulting in fat malabsorption and weight loss as a consequence. Although two previous RCTs showed some beneficial effects of orlistat in patients with NASH, it is not clear if the benefit was related to weight loss conferred by the drug or direct effect.[97,98] Therefore, the drug use should be selected for individual patients as per the clinician's discretion and situation.

Lorcaserin: This is an appetite suppressant associated with about 4 % weight loss in 12 months when combined with lifestyle changes.[99] Pooled data from three lorcaserin RCTs showed that there was modest reduction in ALT levels and improvement of cardiovascular outcomes in treated patients with NAFLD compared to placebo.[100]

Naltrexone/bupropion combination: This drug combination is associated with a weight loss of approximately 5%. Modest reductions in hepatic aminotransferase levels were observed in patients who lost > 10% weight in 12 months with higher dose of the combination.[101]

Phentermine/topiramate: This combination is also associated with significant weight loss benefit and may be associated with improvement of NAFLD.[102]

Liraglutide: High-dose liraglutide treatment (3 mg daily) has been approved by the United States' Food and Drug Administration and the European Medicine Agency recently for primary management of obesity in patients without diabetes. About 8.5% weight loss has been observed in the treated patients compared to placebo in a major clinical trial, although the data on NAFLD was not available in this study.[103] However, another recent phase 2 clinical trial reported significant improvement of liver histology when 1.8 mg liraglutide was administered to patients.[104] Therefore, high-dose liraglutide treatment also may be associated with the same benefit.

Other novel agents: Pentoxyphylline is a competitive nonselective phosphodiesterase inhibitor which raises cyclic adenosine monophosphate and inhibits tumour necrosis factor-a. Both animal studies and clinical trials in humans showed beneficial effects of this novel agent.[82,83,105] Although prebiotics and probiotics have been claimed to be useful in the treatment and prevention of patients with obesity and NAFLD, inadequate supporting data from high-quality clinical studies is against recommendation of the use of these medications in normal clinical practice.[106] Obeticholic acid (OCA) is a synthetic bile acid and agonist of farnesoid X receptor (FXR) that has been recently developed for treatment of primary biliary cirrhosis and has shown promise in the management of NAFLD.[107] FXR is an important nuclear receptor involved in the regulation of bile acid, glucose and cholesterol homeostasis in the human body.[102] Both animal and human studies showed beneficial effects of OCA in the management of NAFLD.[107] Another novel agent elafibranor, a PPAR-a/d agonist, was shown to improve NASH without fibrosis worsening in patients with moderate or severe NASH compared to placebo in a recent clinical trial.[108] The drug is well tolerated and yields improved cardiometabolic risk profile in patients.

Bariatric surgery: Obese patients undergoing bariatric surgery showed significant improvements in both histological and biochemical parameters of NAFLD in a recent meta-analysis.[109] Histological features of the disease, such as steatosis, fibrosis, hepatocyte ballooning and lobular inflammation, as well as reduction in the liver enzyme levels including ALT, AST, alkaline phosphatase and g-glutamyl transferase were observed in patients who underwent surgery. In 2015, based on level B evidence, the Japanese Society of Gastroenterology in cooperation with the Japan Society of Hepatology recommended weight loss surgery as an effective treatment option for patients with NAFLD/NASH complicated by severe obesity for improving fatty changes in the liver and inflammation associated with NASH.[110] Although there is no clear global consensus from different professional bodies on the indications for recommending metabolic surgery in patients with NAFLD, rapidly emerging evidence may lead us towards such a consensus in near future. The most recently published data from the STAMPDE clinical trial that revealed remarkable improvements in the parameters of metabolic syndrome following bariatric surgery is a good example of such high-quality evidence.[111]

Liver transplantation

Recent data suggests that NASH-related end-stage liver disease is the third leading cause for hepatic transplants in the United States and is expected to become the most common cause for liver transplant in 1–2 decades because of the obesity epidemic.[112] The upward global trend in the prevalence of obesity is expected to cause the same health burden in most other regions of the world in the near future. Therefore, liver transplants would become a standard treatment option in a significant proportion of patients with advanced stages of

NAFLD. Based on level B and strength 2 evidence, the Japanese Society of Gastroenterology in association with the Japan Society of Hepatology recommend liver transplant for patients with advanced NASH hepatic failure.[110]The overall survival rates after hepatic transplantation in these patients are almost identical to those receiving transplants for liver failure from other hepatic disorders. However, almost one-third of patients who receive liver transplant for NASH will have recurrence of the disease in the transplanted liver in the absence of intense post-transplant lifestyle modifications [113,114]

Prognosis: NAFLD is described in close relation to the universal obesity epidemic, that is to say, the process has a metabolic basis and its severity varies. FLD has a good prognosis, but patients who do not correct their metabolic problem tend to have an unfavourable evolution. By contrast, patients with NAFLD may progress to cirrhosis and develop HCC. The age and the presence of inflammation in the initial biopsy were independent predictors of NAFLD lesion progression to advanced fibrosis and cirrhosis[115]. In patients with cirrhosis secondary to NAFLD, HCC and hepatocellular failure are leading causes of morbid-mortality. The cumulative rate of development of HCC was 11.3 %, with a survival rate after 5 years of 75.2 %. The cumulative proportion of HCC recurrence after a 5-year follow-up period was 72.5 %. The conclusions drawn from these data are of paramount importance and show the need for protocol monitoring of patients with NAFLD for the prevention of cirrhosis complications, with endoscopy in order to evaluate the formation of oesophageal varices and with ultrasound for early diagnosis of HCC [115].

NAFLD has an increased risk of cardiovascular disease-related death and may indicate future cardiovascular events, independently of sex, age, LDL (low-density lipoprotein)-cholesterol levels and tobacco consumption. There are multiple studies linking elevated liver enzyme levels (mainly gamma-GT) with high risk of stroke or heart disease. Hoorn's study of a cohort of Caucasian population between 50-75 years found an increased risk of heart disease or cardiovascular disease or related to ALT elevations over baseline [116]. A recent study showed that patients with NAFLD have a significantly increased risk of cardiovascular and kidney disease [117], even in patients transplanted for NAFLD. There is an abundance of basic and prospective clinical studies on the activity of pentraxin 3 (PTX3) in relation to the inflammatory processes associated with cardiovascular diseases. Its primary expression is arteriosclerotic lesions and in-depth investigation is underway to see if plasma concentrations are valid for use as a new biomarker of cardiovascular inflammation [118]. In regard to patients with NAFLD, there are no results at present although an abundance of research in this line of study exists.

Conclusion

There has been an exponential increase in the global incidence and prevalence of NAFLD because of the obesity pandemic. In the absence of therapeutic interventions, significant proportion of cases progress to NASH, with increased morbidity and mortality. Diagnosis of NAFLD often depends on biochemical and radiological investigations, as early stages of the disease are often clinically silent. Management of the disease primarily depends on intense lifestyle changes to lose weight. Insulin sensitizers, antioxidants, incretin-based drugs, lipid lowering agents, weight loss medications, bariatric surgery and liver transplantation are therapeutic options that can be added to lifestyle interventions when necessary for management of cases. Continued research for optimizing management strategies of this common disorder is important for reducing the global burden of NAFLD.

Abbreviations

DM2: Diabetes mellitus type 2.
NASH: Non alcoholic steatohepatitis.
NAFLD: Non alcoholic fatty liver disease.
VLDL: Very low density lipoprotein.
FLD: Fatty liver disease.
AST: A spartate aminotransferase.
ALT: Alanine aminotransferase.
HCC: Hepatic cell carcinoma.

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