Pathogenesis, diagnosis, complications and treatment of non-alcoholic fatty liver disease

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Abstract

Number of non-alcoholic fatty liver disease (NAFLD) cases is increasing over time due to alteration of food habit, increase incidence of metabolic syndrome, and lack of exercise. Liver biopsy is the test for diagnosis and staging of NAFLD, but nowadays several biochemical markers, scoring systems, and imaging studies are available to diagnose and stage NAFLD which is linked to end-stage liver disease, hepatocellular cancer, and elevated cardiovascular- and cancer-related morbidity and mortality. Therefore urgent diagnosis and management are required to avoid complications related to NAFLD. This study summarizes the latest evidence on the epidemiology, natural history, pathogenesis, diagnosis and management of NAFLD.

Keywords: NAFLD, NASH, Hepatic fibrosis, recent advances in NAFLD, Non-invasive diagnosis of NAFLD, Medical management of NAFLD

Nonalcoholic fatty liver disease (NAFLD)

Nonalcoholic fatty liver disease (NAFLD) is a leading cause of chronic liver disease, and is strongly associated with the metabolic syndrome. In the last decade, it has become apparent that the clinical burden of NAFLD is not restricted to liver-related morbidity or mortality, and the majority of deaths in NAFLD patients are related to cardiovascular disease (CVD) and cancer [1].

Non-alcoholic fatty liver disease (NAFLD) is currently the most common chronic liver disease in developed countries because of the obesity epidemic. The disease increases liver related morbidity and mortality, and often increases the risk for other co morbidities, such as type 2 diabetes and cardiovascular disease. Insulin resistance related to metabolic syndrome is the main pathogenic trigger that, in association with adverse genetic, humoral, hormonal and lifestyle factors, precipitates development of NAFLD. Biochemical markers and radiological imaging, along with liver biopsy in selected cases, help in diagnosis and prognostication [2]. Intense lifestyle changes aiming at weight loss are the main therapeutic intervention to manage cases. Insulin sensitizers, antioxidants, lipid lowering agents, incretin-based drugs, weight loss medications, bariatric surgery and liver transplantation may be necessary for management in some cases along with lifestyle measures.

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 [3] in experimental trials.

Epidemiology and natural history

NAFLD was largely unknown prior to 1980 but is now recognized as the most common chronic liver disease in the US and many other parts of the world. The prevalence of NAFLD, as determined by population studies using ultrasound and serum enzymes, is estimated at 23%–30%)[4]. The prevalence is expected to increase as the incidence of obesity and type 2 diabetes mellitus increases. While such studies do not distinguish NASH, the progressive form of the disease, from bland steatosis, it has been suggested that the prevalence of NASH is 5.7%–17% of the general population.

NAFLD may lead to NASH, cirrhosis and in some cases, hepatocellular carcinoma.Fifty percent of patients with NAFLD have NASH and 19% have cirrhosis at the time of diagnosis .Once cirrhosis develops 30%–40% of patients will die of liver failure over a 10 year period, a rate that is at least equal to that seen with hepatitis C. Hepatocellular carcinoma is an increasingly recognized outcome[5].

Etiology

The precise etiology of NAFLD is unknown but there is a strong association with obesity, the metabolic/insulin resistance syndrome and dyslipidemia. Most patients with NASH are obese and there is increasing evidence of an obesity epidemic in the US and elsewhere [6]. It is estimated that 70%–80% of obese subjects have NAFLD with 15%–20% having NASH. A recent study demonstrated that 88% of patients with NASH have the insulin resistance syndrome. Type 2 diabetes (DM2) is associated with NAFLD in 30%–80% of subjects and NAFLD is present in virtually 100% of patients with combined DM2 and obesity [7]. In patients with diabetes, the standardized mortality ratio for cirrhosis (2.52) is greater than that for cardiovascular disease (1.34). Dyslipidemia is present in 50%–60% of individuals with NAFLD. Hypercholesterolemia alone is associated with a 33% prevalence.

Natural history

The natural history of NAFLD is not well established, with significant knowledge gaps about the marked inter-individual variations in disease onset, progression, and complications.
NAFLD represents a wide spectrum of clinical entities from asymptomatic hepatic steatosis to more advanced liver disease with hepatic failure or hepatocellular carcinoma (HCC).The rate of disease progression in most cases is slow, although rapid development of advanced liver disease may be occasionally found. About one-third of people eventually develop NASH; [8] however, regression of fibrosis is also noticed in about 20% of these cases.

Pathogenesis

The pathologic sequence of events from steatosis (ie, the “first hit”), to steatohepatitis to cirrhosis is well established However, fat, per se is not hepatotoxic [9]. It is now widely accepted that a “second hit” is necessary for NAFLD to progress to NASH and cirrhosis.

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 [10]. 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.

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 [11].Because of the very strong association with MS, NAFLD is considered as the hepatic component of MS.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).

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). High hepatic VLDL output also results in high circulating triglycerides and LDL and low circulating high density lipoprotein (HDL) levels that increase atherosclerosis risk. An increased glucagon level with altered insulin/glucagon ratio is seen in patients with NAFLD.

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. Glucagon-like insulinotropic peptide-1 (GLP-1), ghrelin, selenoprotein P, leptin, adiponectin and the myokines are some of these chemicals. Physical activity stimulates production of various soluble chemicals from muscle fibres, collectively termed as myokines, that show auto, para and endocrine functions [12].

These myokines function as messengers between skeletal muscle and other tissues, such as liver, adipose tissue, heart, brain and blood vessels, signalling 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.31 However, there are studies showing increased levels of irisin in patients with metabolic syndrome and NAFLD [13].

Diagnosis

Liver biopsy is the gold standard test for diagnosis, grading, and histological assessment of NAFLD, and a four point histopathologic grading system is used to assess severity of steatosis that ranges from 0 to 3, depending on presence of the percentage of fat-containing hepatocytes [14]. But the value of a liver biopsy for the diagnosis of NAFLD in routine clinical practice is controversial, especially in the presence of a generally good prognosis for most patients with NAFLD, the lack of an established form of effective therapy, and the risks and costs associated with the liver biopsy.

Non-invasive tests for diagnosis of hepatic steatosis
Imagings for diagnosis of hepatic steatosis

A. **Abdominal ultrasonography**: Usually, "Hepatic steatosis" is diagnosed incidentally by abdominal ultrasonography (USG) which detect the increased echogenicity of the liver and divides fatty liver into three grades [15]. To identify hepatic steatosis, USG has sensitivity from 60 to 94% and specificity from 84 to 95%, and sensitivity is more than 90% when liver biopsy shows > 20% steatosis. Hepatorenal index of 1.34 or higher has sensitivity of 92% and specificity of 85% for identifying steatosis > 5% [16]. Another semiquantitative score (ultrasonographic fatty liver indicator) which requires the presence of liver/kidney contrast (brighter liver than kidney) among other parameters can detect NAFLD when score ≥ 2. USG has several advantages (non-invasive test, widely available, low cost, quick diagnosis) and disadvantages (degree of fibrosis cannot be detected, low sensitivity when steatosis is less than 20%, and limited use in obese individuals) for detection of fatty liver.

B. Controlled attenuation parameter: Transient elastography is an ultrasound-based study and also known as vibration-controlled transient elastography or Fibroscan which can measure controlled attenuation parameter (CAP). CAP which ranges from 100 to 400 decibels per meter (dB/m) can detect significant hepatic steatosis, but it is less accurate to distinguish between the different grades of hepatic steatosis [17]. However other studies indicate that CAP score is well correlated with steatosis grades in real-world clinical practice. The optimal cut-off values of CAP for estimation of hepatic steatosis grades such as S1, S2, and S3 are ≥ 263dB/m, ≥ 281dB/m and ≥ 283dB/m respectively

C. Computed tomography (CT scan): Decreased attenuation of hepatic parenchyma compared to intrahepatic vessels, spleen, and kidney is detected in NAFLD by both contrast-enhanced and noncontrast CT scan. When hepatic density is higher than spleen, hepatic steatosis can be excluded.

D. Magnetic resonance imaging (MRI): MRI is considered as the most definitive imaging study for qualitative and quantitative assessment of hepatic steatosis. The sensitivity and specificity of MRI to detect histologically confirmed hepatic steatosis are 76.7 to 90.0% and 87.1 to 91%, respectively [18].

Frequency selective MRI, chemical shift encoded MRI, MR spectroscopy, and magnetic resonance elastography techniques are usually used to assess hepatic fat content [19]. In MRI, both in-phase (IP) and out-of-phase (OOP) imaging to be adequately assessed to detect fatty liver (FL), and in out-ofphase image FL appears as hyper intense (in T1 image), mildly hyper intense (in T2 image), and signal droop out (signal loss is demonstrated when there is 10–15% fat fraction with maximum signal loss occurring when there is 50% fatty infiltration of the liver).

Advantages of MRI-based detection of fatty liver are no radiation exposure; high diagnostic accuracy; can detect fat as low as 5–10%; operator independent; highly responsive to changes in steatosis throughout parenchyma; and not significantly impacted by demographics, histologic activity, or co-existing hepatic conditions. It has the following disadvantages: high cost and taking long time.

Hydrogen-1 MR spectroscopy (1H-MRS) is a noninvasive technique which can diagnose and quantify hepatic steatosis into three grades, and H-MHS thresholds correspond with histopathologic grading of steatosis and may obviate liver biopsy [20]. 1H-MRS allows the direct measurement of the area under the lipid resonance peak. This test result is not modified by the presence of confounding factors such as fibrosis, iron overload, and glycogen. Main drawbacks of H-MHS are high cost, less availability, complex technique requiring patient cooperation, samples only a small portion of the entire liver, and not well validated and still considered a research tool. Proton density fat fraction (PDFF) in MRI is also used for quantifying hepatic steatosis. PDFF is an accurate marker of hepatic steatosis and allows discriminating with a good diagnostic accuracy between different grades of hepatic steatosis [21].

The accuracy of PDFF measurement using chemical shift-encoded methods is similar to that of MRS. Recently; hepatic phosphorus-31 MRS (31P-MRS) is proposed in different studies as a potential marker to detect distinct biochemical changes in different NAFLD states. It shows promise in the differentiation of NAFLD stages.

E. Xenon–133 liver scan: Xe-133 liver scan is a safe, reliable, non-invasive method with low radiation exposure to detect and quantify hepatic steatosis, and is superior to ultrasound with a sensitivity of 94.3% and specificity of 87.5% [22]. Compared with other imaging investigations, Xe-133 scan is more accurate to detect mild grade of steatosis . One major limitation of Xe-133 scan is that it only detects fat; therefore, it is not expected to distinguish between different subtypes of NAFLD and does not provide information of liver morphology. The usefulness of Xe-133 scan in the diagnosis of NAFLD has not been well studied till now.

Non-invasive scoring systems for diagnosis of hepatic steatosis : There is no single laboratory marker that can be used for the diagnosis of NAFLD. Gamma-glutamyltransferase (GGT) in the serum is frequently elevated in NAFLD patients and associated with increased mortality [23], however does not help in diagnosis of NAFLD. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels are not sensitive for diagnosis of NAFLD. Following scoring systems are available to identify NAFLD.

Complications

Cardiovascular Disease

Cumulative studies using subclinical markers of CVD show that patients with biopsy-proven NAFLD, and in particular NASH, exhibit endothelial dysfunction, impaired left ventricular diastolic dysfunction/energy metabolism,12-14 increased carotid intima-media thickness [24] and show a higher prevalence of carotid atherosclerotic plaques compared with patients without NAFLD.Three large cross-sectional studies (total >20,000 participants) from East Asia reported that ultrasound (USS)-defined NAFLD is independently associated (after adjustment of other CHD risk factors) with the presence of coronary artery disease.

NAFLD are at greater risk of having concomitant CVD than those without NAFLD.
Type 2 Diabetes (T2DM) by 2030, the estimated prevalence of diabetes worldwide is expected to exceed 500 million people, of which 90% will be attributed to T2DM due to the aging population and rapidly rising numbers of obesity. Of concern, T2DM is associated with a 2-fold risk of

chronic liver disease secondary to NAFLD, cirrhosis, and HCC. The relationship between NAFLD and T2DM, however, is complex. A diagnosis of NAFLD (mainly on imaging) in patients with established T2DM is strongly associated poor glycemic control, proliferative retinopathy,38 increased prevalence of cardiac/kidney disease,21 and a 2.2-fold increase in -cause mortality compared to patients without NAFLD [24].

Kidney Disease

CKD is a leading public health concern, with hypertension and diabetes being two major risk factors. The prevalence of CKD now stands at 4.3%-13% in the general population,59,60 but is expected to increase by 7% annually.[25] the high morbidity, mortality, and healthcare costs associated with CKD have led to investigators attempting to identify new modifiable risk factors. This is evident by an increasing number of studies evaluating the hypothesis that NAFLD may be an independent risk factor for CKD.

Endocrinopathies

Several endocrinopathies have been associated with NAFLD, including growth hormone deficiency, hypogonadism, hypopitiutarism, polycystic ovarian syndrome, hypercortisolemia, and hypothyroidism. However, data in this field remain limited. Outside case series/retrospective cohort studies,no prospective study has evaluated the temporal relationship between NAFLD and these conditions, and the majority of studies have simply evaluated the prevalence and/or severity of NAFLD as a consequence of endocrinopathies [26].

Hypothyroidism.

[27] found that biopsy-proven NAFLD is associated with a higher prevalence of hypothyroidism (21% versus 9.5%) compared with controls matched for age, sex, ethnicity, and BMI. Furthermore, they found a significant association of NASH and hypothyroidism, independent of T2DM, dyslipidemia, hypertension, and age. This was confirmed in a larger study of over 2,000 patients with hypothyroidism.90 Here the authors reported that overt and subclinical hypothyroidism (even in the range of normal thyroid stimulating hormone [TSH] levels) are both associated with NAFLD, independent of known metabolic risk factors.

Polycycstic Ovarian Syndrome (PCOS)

Studies suggest that patients with PCOS are at risk of NAFLD, independent of BMI. It is unclear, however, if the converse is true. Nevertheless, a cross sectional study from Australia reported that 71% (10/ 14) of patients with USS and/or biopsy-proven NAFLD (age 20-45 years) had PCOS, which is significantly higher than the average prevalence (6%- 10%) of a matched American female population.

[28] recommended a two-stage approach in screening individuals with NAFLD for OSAS; namely, an Epworth Sleepiness Scale questionnaire followed by nocturnal monitoring in those who have high-risk scores. It should be noted, however, that screening questionnaires for OSAS have relatively poor sensitivity/specificity and have not been validated for use in patients NAFLD.

Osteoporosis

Accumulating data supports an inverse relationship between obesity (and NAFLD) and low bone-mass density (BMD)/osteoporotic fracture. In a cross sectional study of 481

postmenopausal Korean women, [29] found that individuals with USS defined NAFLD had an increased independent risk of lower BMD (using dual-energy x-ray absorptiometry). The significance remained after adjustment for BMI, smoking, age, alcohol, and the metabolic syndrome. This risk does not appear to be sex-specific, as a large Chinese questionnaire-based study (n > 7,000) recently reported that male patients with USS defined NAFLD were 2.5 times more likely to have osteoporotic fractures than those without NAFLD. Of concern, these risks are not restricted to adults. [30] highlighted that children with biopsy-proven NAFLD (even as young as 10 years old) have a higher incidence of low BMD than age- and weight-matched controls (45% versus 0%). Furthermore, children with NASH had lower BMD than those with simple steatosis.

Treatment

Treatment falls into two categories: targeting either the steatosis or the pathogenesis of progression. There are no FDA approved pharmacologic agents and, in fact, no FDA guidelines for such drugs despite the fact that NAFLD are the most common liver disease in the US. Virtually all are compromised by small numbers and lack of placebo control. Treatment of steatosis/insulin resistance

The treatment of steatosis is inexorably linked to obesity, insulin resistance and dyslipidemia. In general, factors that decrease steatosis consist of weight loss or pharmacologic therapy directed at insulin resistance or dyslipidemia [31]. The treatment of steatohepatitis is directed at oxidative stress, infl ammation and fi brosis. Factors that decrease oxidative stress and infl ammation include antioxidants, probiotics, anti-cytokines and glutathione precursors. Anti-fibrotic therapy is in its infancy.

Weight loss

Weight loss improves liver chemistries, steatosis, necroinflammatory changes and fibrosis [32] Furthermore, gradual weight reduction has been shown to lower insulin levels and improve quality of life. Weight loss may be achieved through diet and exercise or bariatric surgery.

Diet

The ideal diet and rate of weight loss is yet to be determined although it is known that rapid weight loss may exacerbate disease [33].A number of studies, both controlled and uncontrolled, indicate that weight loss decreases hepatic steatosis. The durability of weight loss on hepatic steatosis remains to be determined. Low fat diets should be avoided. Some have suggested that a Mediterranean diet (ie, high consumption of complex carbohydrates and monounsaturated fat, low amounts of red meat, and low/moderate amounts of wine) is preferred. A low glycemic, low calorie diet with a weight loss of 1–2 kg/wk seems reasonable.

Bariatric surgery

Bariatric surgery, recently reviewed has proved successful in a number of studies [34]. The formerly used ideal surgery was, however, associated with fatty liver and even hepatic failure.The durability of bariatric surgery has yet to be determined but it seems likely to be the only therapy that will change the natural history of NASH.

Orlistat

Orlistat is a lipase inhibitor that promotes weight loss by reduction of fat absorption. A trial by [35] in 10 patients reported a mean weight loss of 10 kg with 6 months of treatment. Aminotransferases improved during treatment. No change in histology was reported. Another double blind, placebo-controlled trial randomized 52 patients with NAFLD (diagnosed by ultrasound and confirmed with biopsy) to orlistat or placebo for 6 months. Orlistat decreased aminotransferase levels and reversed fatty liver as determined by ultrasound.

Sibutramine

Sibutramine, an appetite suppressant, is a serotonin reuptake antagonist approved for weight loss. It also has been studied in patients with NAFLD. It significantly improved aminotransferases in 13 of 13 patients and decreased evidence of hepatic steatosis on ultrasound in 11 of 13 patients in an open label, nonrandomized study [36].These patients were all obese and were diagnosed with NASH. Alkaline phosphatase levels increased during therapy.

Pharmacologic therapy

Thiazolidinediones

Thiazolidinediones (TZDs) are PPARγ agonists which increase insulin sensitivity and increase the number and activation of adipocytes [37]. This leads to a redistribution of lipids from liver and muscle cells to adipocytes which, in turn, restores insulin sensitivity. They also increase adiponectin expression, decrease TNFα expression, and reduce collagen synthesis .The net effect of PPARγ agonists is an increase in insulin sensitivity, a redistribution of fat from liver to adipocytes and a reduction in hepatic fi brosis. Animal studies have confirmed these observations and human trials are beginning to confi rm the beneficial effects In the initial study using troglitazone, 7 of 10 patients showed improvement in ALT after 6 months. There was, however, no histologic improvement and troglitazone was removed from the market because of hepatotoxicity. Subsequent trials with pioglitazone and rosiglitazone have not shown evidence of hepatotoxicity.

Conclusions

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.

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Table 1 Causes of non-alcoholic fatty liver disease

Nutritional Drugs	Nutritional Drugs
Starvation Glucocorticoids Obesity* Tamoxifen Bariatric surgery Amiodarone Parenteral nutrition Valproic acid Celiac disease Zidovudine Metabolic Didanosine Insulin resistance* Other Dyslipidemia* Infl ammatory bowel disease Fatty liver of pregnancy	Starvation Glucocorticoids Obesity* Tamoxifen Bariatric surgery Amiodarone Parenteral nutrition Valproic acid Celiac disease Zidovudine Metabolic Didanosine Insulin resistance* Other Dyslipidemia* Infl ammatory bowel disease Halogenated hydrocarbon Toxic mushrooms

* Most common causes

Table 2 Types of NAFLD by histology and outcome

Category Histology Outcome	**Category Histology Outcome**	**Category Histology Outcome**
Type 1	steatosis only	non progressive
Type 2	steatosis plus lobular inflammation	benign course
Type 3	Steatosis and ballooning degeneration	lobular infl ammation NASH without fibrosis may progress to cirrhosis
Type 4	steatosis, ballooning degeneration with Mallory cirrhosis	NASH, may progress to bodies and/or fi brosis

Fig-1 Pathogenesis of nonalcoholic fatty liver disease and effects of various therapeutic interventions

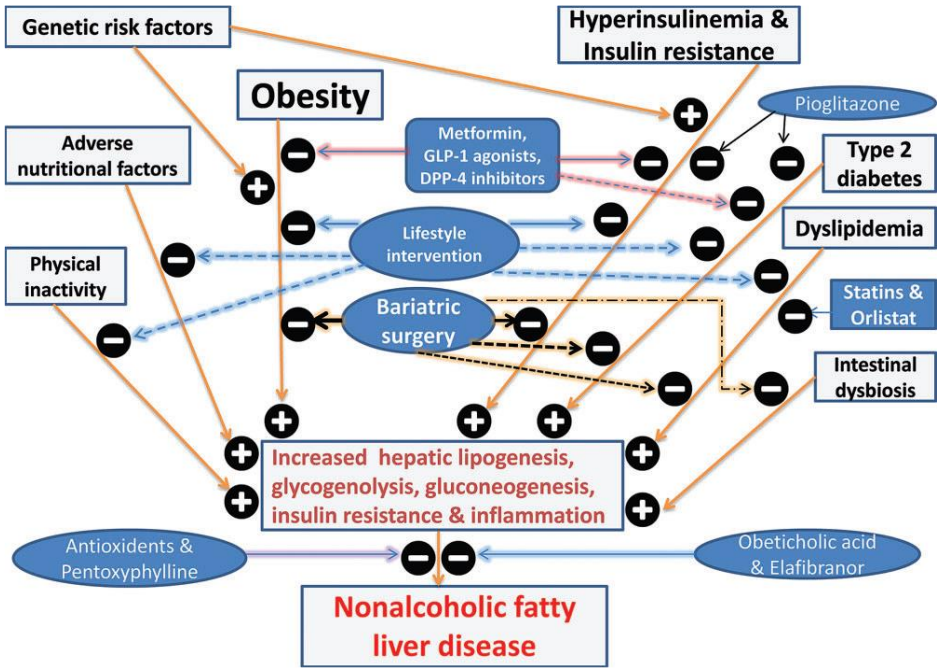

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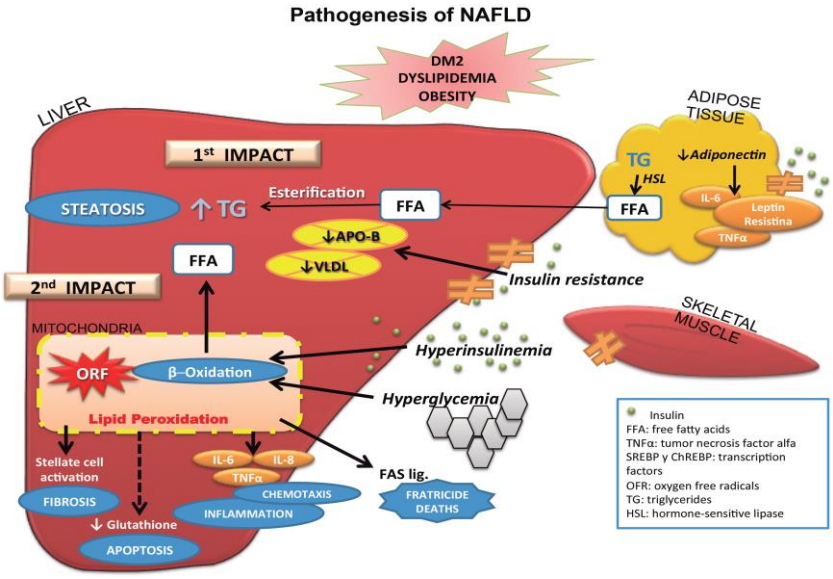
Fig-2 Pathogenesis of NAFLD (author: Verónica Martín



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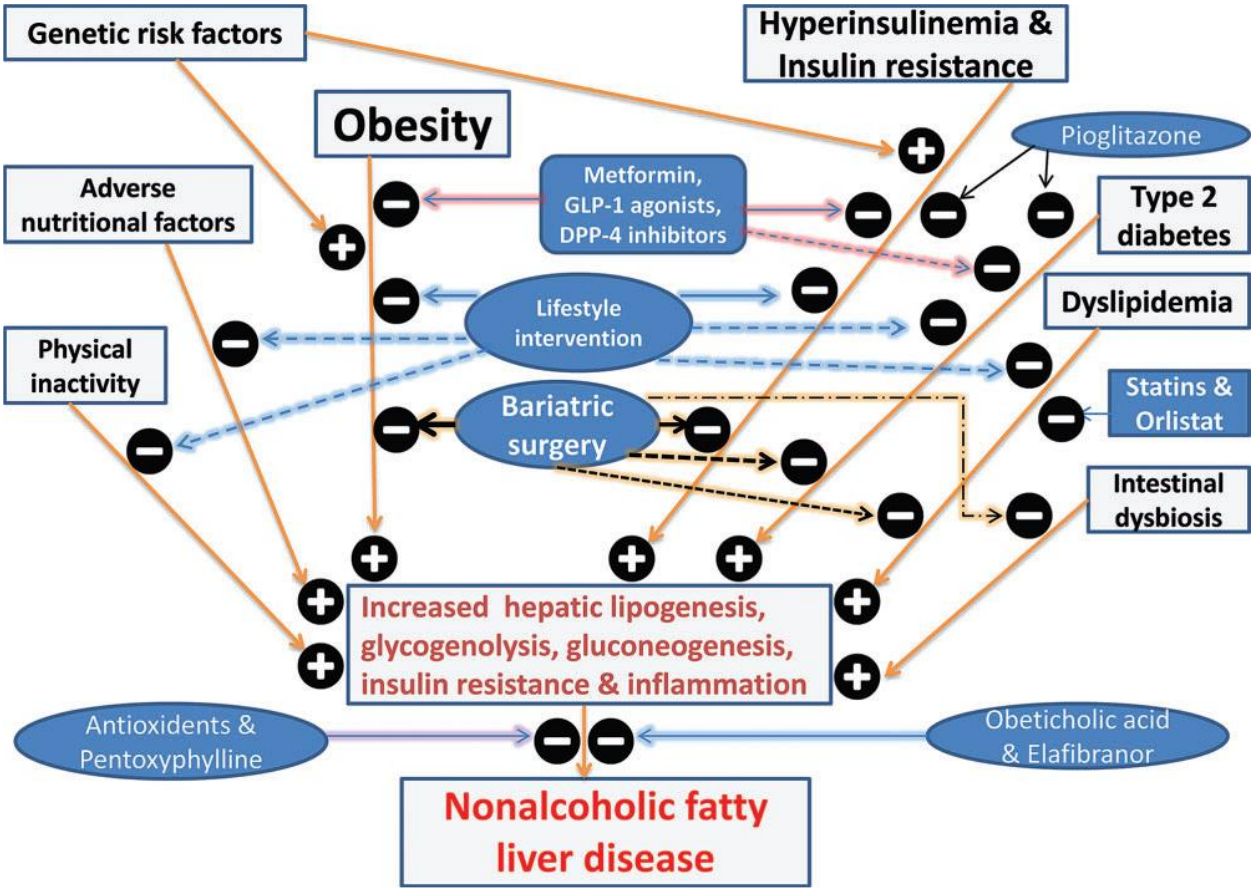
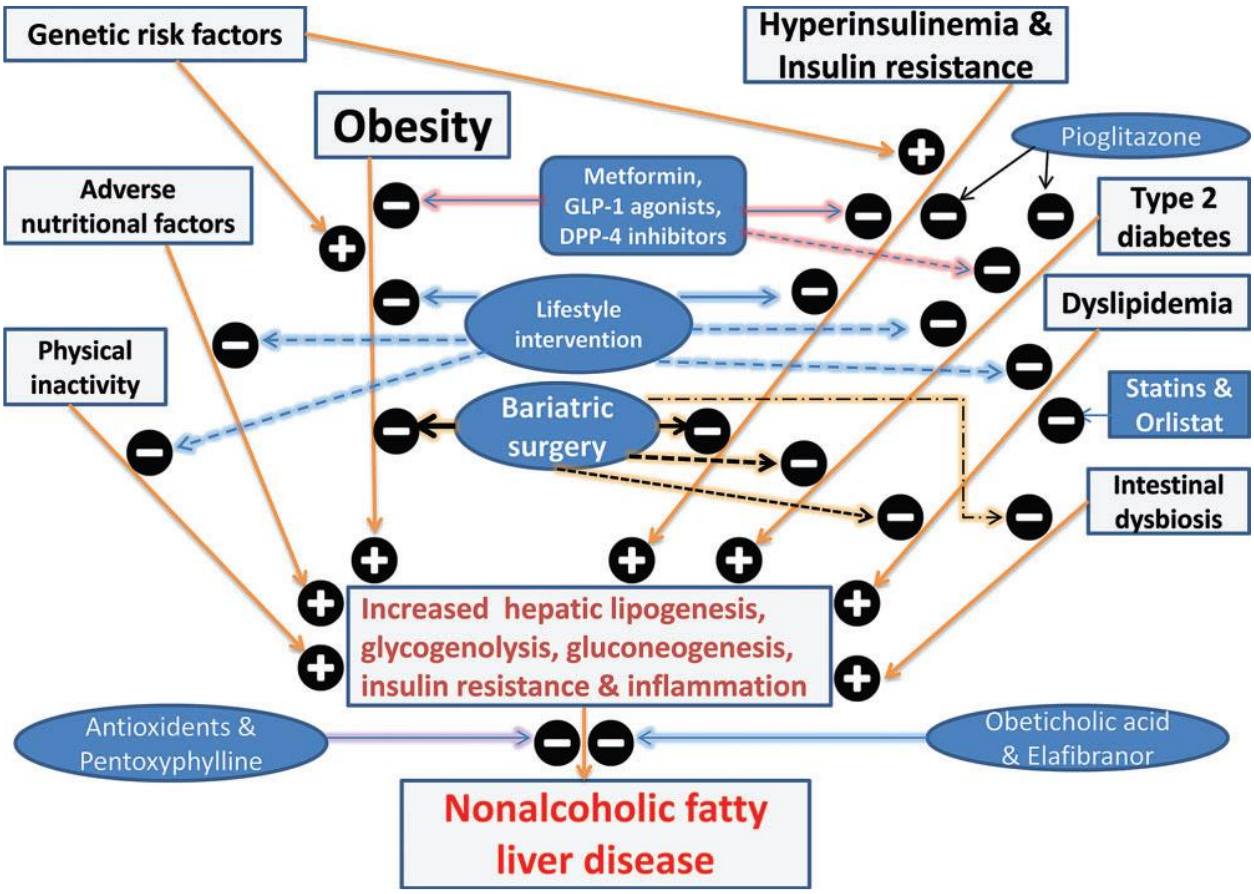

Genetic risk factors
Hyperinsulinemia & Insulin resistance
Obesity
Pioglitazone
Adverse nutritional factors
Metformin, GLP-1 agonists, DPP-4 inhibitors
Type 2 diabetes
Lifestyle intervention
Dyslipidemia
Physical inactivity
Statins & Orlistat
Bariatric surgery
Intestinal dysbiosis
Increased hepatic lipogenesis, glycogenolysis, gluconeogenesis, insulin resistance & inflammation
Antioxidents & Pentoxyphylline
Obeticholic acid & Elafibranor
Nonalcoholic fatty liver disease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