Nonalcoholic fatty liver disease in children living in the obeseogenic society

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Background: **The problem of obesity in children has grown considerably in recent years in the United States as well as the rest of the world. This has resulted in a marked increase in the prevalence of nonalcoholic liver disease in the pediatric age group. Nonalcoholic fatty liver disease (NAFLD) is currently the most common hepatic disorder seen in pediatric hepatology practice.**

Data sources: **We have reviewed the most recent literature regarding the prevalence, pathogenesis as well as the most recent advances in the diagnostic and therapeutic modalities of NAFLD in children.**

Results: **NAFLD affects a substantial portion of the population including children.**

Conclusions: **The rising incidence of NAFLD, nonalcoholic steatohepatitis (NASH) and cirrhosis emphasizes the need for effective treatment options. The lack of complete understanding of the pathogenesis of NAFLD still limits our ability to develop novel therapeutic modalities that can target the metabolic derangements implicated in the development of the disorder.**

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Introduction

The problem of obesity in children has grown considerably in recent years in the United States as well as the rest of the world and has reached frightening figures. Unless obese children adopt healthy patterns of eating and exercise, they are much more likely to become overweight adults.

Obesity has been established as a major risk factor for diabetes, hypertension, cardiovascular disease and some cancers in both men and women. Other complications include sleep apnea, osteoarthritis, infertility, idiopathic intracranial hypertension and gastroesophageal reflux disease. The annual cost to society for obesity is estimated at nearly $100 billion and is responsible for over 300 000 deaths each year.

Chronic liver disease associated with obesity was first reported in the late 1970s in obese pregnant women.[1] The histological changes in these patients were similar to the histological features seen in patients who are heavy alcohol drinkers. Therefore, the disorder was initially called nonalcoholic steatohepatitis (NASH). Recently a new term, nonalcoholic fatty liver disease (NAFLD), has come to use as it encompasses a spectrum of hepatic pathological changes ranging from fatty liver (steatosis) to cirrhosis. NASH is an intermediate form of liver damage that may progress to cirrhosis.

Steatohepatitis as a cause of chronic liver dysfunction in obese children was first reported in the early 1980s.[2] The authors described 3 American children with steatosis and steatohepatitis. However, until recently NAFLD was considered to be a disease of adults. It has been realized that NAFLD can also affect children and has been increasingly recognized as an important pediatric liver disorder.

Pathogenesis

Despite the progress we made in the study of NAFLD, the pathogenesis of NAFLD remains poorly defined and we still lack a complete understanding of the mechanisms involving in the progression from steatosis to NASH and cirrhosis.

Current theory suggests a "two hit" process. Disorders of the hepatic uptake, synthesis, degradation, and secretion of free fatty acids will lead to accumulation of lipids in the hepatocytes resulting in macrovesicular steatosis. These changes will make the

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liver susceptible to a second hit which may result in inflammatory changes and disease progression.[3]

Excessive adiposity in patients with metabolic syndrome contributes to tissue damage. Fat-derived factors such as fatty acids, adiponectin, and tumor necrosis factor (TNF) alpha regulate the inflammatory response and promote NAFLD by modulating the hepatic inflammatory response. Adiponectin inhibits fatty acid uptake, stimulates fatty acid oxidation and lipids export, and enhances hepatic insulin sensitivity. On the other hand, TNF recruits inflammatory cells to injured tissues and promotes insulin resistance. Adiponectin and TNF alpha are mutually antagonistic and inhibit each other's production and activity. In patients with metabolic syndrome there is cytokine imbalance with increased production of TNF with reduced activity of adiponectin. The combination of high TNF levels and low adiponectin levels will result in insulin resistance with fat accumulation, inflammation and cell death.[4,5]

Epidemiology

The exact prevalence of NAFLD is not known because of the lack of accurate noninvasive diagnostic modalities. Although imaging methods can diagnose fatty changes, they lack sensitivity in patients with mild steatosis and fail to differentiate steatohepatitis from simple steatosis.[6] The prevalence of NAFLD ranges from 9% to 36.9% worldwide in patients with unknown risk factors.[7-9] In the United States, the percentage of subjects with unexplained high liver enzymes and therefore presumed to have NAFLD has been reported to be 23% of the population which is double the percentage reported in a previous report.[10] No information is available regarding the prevalence of NASH in unselected population (subjects without known risk factors) because of the need for liver biopsy to establish the diagnosis which is not an accepted screening method. The prevalence of NAFLD is much higher in subjects with known risk factors. The prevalence of NAFLD in patients with metabolic syndrome is higher than in patients without.[11] The prevalence of NAFLD in morbidly obese patients undergoing bariatric surgery was reported to be as high as 96%,[12] while the prevalence of NASH in the same group ranges from 12% to 25%.[12,13]

NAFLD is a disease of all ages. It has been reported in children as young as 2 years of age. In adults, the prevalence of NAFLD increases with age. The peak prevalence is earlier in men (fourth decade) than in women (sixth decade), which may be explained by the protective effects of estrogen. In children the majority of patients are diagnosed during the second decade of life. The exact prevalence of NAFLD in children is unknown. The prevalence of fatty liver diagnosed by ultrasonography in 810 school children from northern Japan was found to be 2.6%. The study shows a strong correlation of NAFLD with indices of obesity such as BMI.[14] In the National Health and Nutrition Examination Survey, cycle 111 (NHANES 111) in the USA, serum alanine aminotrasferase (ALT) and gamma-glutamyl transpeptidase were measured in 2450 obese and overweight children. In this study, 6% of overweight, and 10% of obese adolescents had an elevated ALT, but alcohol use could not be excluded.[15]

Early reports suggested that NAFLD is more common in females, however, more recent studies reported equal numbers of either sexes or a higher male proportion. In the largest pediatric report, 77% of NAFLD patients were males.[16] On the other hand, all published pediatric reports showed that males outnumber females in an approximately 2:1 to 3.5:1 ratio.[17-22]

NAFLD seems to be more common in Hispanics with a higher prevalence in non-Hispanic whites than in non-Hispanic blacks. Racial and ethnic differences are expected among patients with NAFLD. Obesity and type 2 diabetes are the two major risk factors for NAFLD. Obesity is more prevalent in non-Hispanic black and Mexican-American women than in non-Hispanic whites.[22,23] Similarly, type 2 diabetes is more commonly diagnosed in non-Hispanic black and Mexican-American men and women compared to non-Hispanic whites.[24] Metabolic syndrome which is a well-established risk factor of NAFLD is seen more often in Hispanics than in non-Hispanic blacks and whites.[25] Patients with metabolic syndrome have a 4 to 11 fold increased risk to develop NAFLD and are less likely to show disease regression.[26] Moreover, Hispanic males have higher body fat and percentage fat than white and black males.[27]

Clinical picture

The majority of patients with NAFLD are asymptomatic.[28] Occasionally patients may complain of mild right upper quadrant abdominal pain, fatigue and malaise. Most patients are diagnosed after the detection of high serum aminotransferase level during a routine laboratory testing or abnormal hepatic imaging performed for different reasons such as abdominal pain or suspected gall stones. Physical examination of patients with NAFLD is basically normal except for acanthosis nigricans which is usually seen at the nape of the neck, axilla, and groins or over the knuckles. Hepatomegaly may be felt in 75% of the adult patients. Patients with advanced liver disease may present

with jaundice, pruritus, ascites, spider angiomatas, splenomegaly, hard liver border, palmar erythema, or asterixis. Most patients have manifestations of metabolic syndrome including obesity, diabetes, hypertension and dyslipidemia.[29]

Diagnosis

Liver biopsy

Liver biopsy is the gold standard for diagnosing NAFLD since it can be diagnosed in adult patients with only 50% accuracy depending on clinical parameters.[30] Liver biopsy is also the only method that can differentiate steatohepatitis and fibrosis from simple steatosis. Given the high prevalence of this disorder in the general population, the question whether or not to do a liver biopsy is commonly raised. Arguments against liver biopsy include cost, sampling error, variability of pathological interpretation, the benign nature of the disorder in the majority of patients, the lack of effective therapy, morbidity and mortality. Many clinicians are reluctant to perform liver biopsy in patients suspected to have NAFLD and the diagnosis in many cases is based on clinical background and imaging studies.

On the other hand, performing liver biopsy will establish the diagnosis, provide prognostic information, assess severity, and motivate the patient and the family to seek treatment. Although trial of weight loss while monitoring liver enzymes has been suggested, normalization of liver enzymes is not necessarily associated with histological improvement. Therefore, another approach adopted by other clinicians is to measure ALT level and perform liver ultrasound. If one or both tests are abnormal they perform liver biopsy, but if both are normal, the risk factors should be corrected if present.

Macro and microvesicular steatosis is the corner stone on which the diagnosis of NAFLD is based. Other histological features include acute and chronic inflammation, cytologic ballooning, and glycogen nuclei of hepatocytes, perisinusoidal fibrosis and Mallory hyaline bodies. Two types of histological features have been described in children: type 1 characterized by steatosis, ballooning degeneration, and perisinusoidal fibrosis, and type 2 characterized by steatosis, portal inflammation, and portal fibrosis.[31]

Laboratory evaluation

In a patient with suspected NAFLD or NASH, initial testing should include levels of aspartate aminotransferase (AST), ALT, total and direct bilirubin, and fasting serum glucose, as well as a lipid panel. Other common causes of elevated liver enzymes should be excluded such as viral and autoimmune hepatitis and metabolic liver diseases including Wilson's disease, hypothyroidism and alpha-1 antitrypsin deficiency. The most common finding is mild to moderate elevation of serum aminotransferases (mean range, 100 to 200 IU/L). Generally, the ratio of AST to ALT is less than 1, but this ratio may reverse with development of fibrosis.[32] Liver enzymes may be normal in children with NAFLD and normal aminotransferases do not exclude the presence of advanced disease.[16] Serum alkaline phosphatase and gamma-glutamyl transpeptidase may also be mildly abnormal. Albumin, bilirubin, and platelet levels are usually normal unless in the presence of cirrhosis. Autoimmune antibodies (antinuclear and anti-smooth-muscle antibody) ferritin and transferrin may be elevated in some patients with NAFLD.[28] The reason for such elevation is still unknown.

Serum markers of fibrosis

Liver fibrosis is a dynamic process involving a complex interaction between several enzymes involved in extramatrix synthesis and degradation. Several extramatrix components have been investigated as potential predictors of fibrosis severity in patients with NAFLD.[33] Serum levels of hyaluronic acid (HA) are increased in patients with hepatic fibrosis due to increased glycogen deposition and decreased sinusoidal clearance.[33] Although levels of HA were found to correlate with bridging fibrosis and cirrhosis,[34,35] they failed to predict milder forms of fibrosis.[34,36] In addition, HA is an acute phase reactant and can be elevated in the context of systemic inflammation which may produce falsely positive results.

Another fibrosis marker is type IV collagen. Serum levels of 7S domain were found to be elevated in Japanese NAFLD patients with severe fibrosis.[37] In a recent study elevated serum levels of laminin (a component of intracellular matrix) were found to be predictive of any form of fibrosis in 30 patients with NAFLD.[36] The measurement of serum levels of other fibrogenic factors such as thioredoxin, TNF-α, adiponectin and leptin has failed to prove a consistent relationship with the stage of hepatic fibrosis.[38-45]

Multiple serum fibrosis markers have been combined in order to produce accurate predictive scores. Fibro test is an algorithm combining gender, age, bilirubin, gammaglutamyl transferase, apolipoprotein AI, haptoglobin and α2-macroglobulin. Fibro Test has been validated in several hepatic disorders.[46,47] However it failed to predict fibrosis in a large proportion of patients with NAFLD.[47] On the other hand, the European Liver Fibrosis Group has investigated the usefulness of combining age with

serum levels of aminoterminal propeptide of type III collagen, hyaluronic acid and tissue inhibitor of matrix metalloproteinase I in predicting hepatic fibrosis in 912 patients with a wide range of liver diseases. The study showed promising results but was limited by the small number of NAFLD patients (only 61 patients). In conclusion, the use of serum markers of fibrosis in the assessment of patients with NAFLD seems to be promising, however this needs further validation. The lack of availability of these tests in most laboratories limits its clinical usefulness.

Radiologic methods

The role of radiologic modalities in the diagnosis, characterization and monitoring of patients with NAFLD has received a considerable attention over the last 2 decades.

Ultrasonography is the most commonly used radiologic modality in patients suspected to have NAFLD.[48-54] Ultrasonic examination of fatty liver usually reveals the characteristic picture of "bright liver" due to increased echogenicity of the liver. Patients with hepatic fibrosis usually have a hepatic coarse echo pattern. Posterior beam attenuation due to decreased ultrasound beam penetration of fatty liver may result in posterior darkness and lack of diaphragm definition. Other features include hepatomegaly, hypoechoic kidney and decreased visualization of hepatic and portal veins secondary to compression of swollen hepatocytes on their walls. Accumulation of fat may also result in abnormal hepatic vein Doppler waveform pattern[55] which may be monophasic or biphasic.[56] Several studies have looked into the sensitivity of ultrasound in detecting steatosis and fibrosis with a wide range of results.[48-53] The sensitivity seems to improve with increased hepatic fatty infiltration with a range of 60% to 90% in patients with moderate hepatic steatosis.[48-54] Another limitation of ultrasonography is subjectivity as it is an operator-dependent procedure.

Computed tomography (CT) has commonly been utilized in the evaluation of patients with fatty liver. There is an inverse correlation between the liver density as measured by CT attenuation and the degree of hepatic fatty infiltration.[57] CT examination may also reveal the presence of mild splenomegaly which is a common finding in patients with NAFLD.[58,59] Disadvantages of CT include limited use in patients with hepatic iron overload and radiation exposure.

Different magnetic resonance imaging (MRI) techniques have been used in the evaluation of NAFLD patients. MRI with conventional pulse sequence seems not to be a sensitive method for the detection of fat deposition in the liver.[60,61] The best results can be obtained with the use of gradient-echo chemical shift technique.[62] A recent study has suggested that fast spin-echo MRI can better quantitate hepatic fat than out-of-phase gradient-echo MRI especially in patients who developed cirrhosis.[63] Quantification of hepatic fat using the spin-echo technique was impractical for use in children due to the length of time needed to complete the study. The development of fast gradient-echo technique has significantly reduced the study time which made the test more suitable for use in the pediatric age group. These techniques have been shown to be able to quantitate hepatic fat content even at near-normal levels.[64,65] Disadvantages of MRI include limited use in patients with hepatic iron overload and it is contraindicated in patients with implantable devices and pace makers and also in claustrophobics.

Localized proton magnetic resonance spectroscopy (MRS) is a noninvasive diagnostic modality which can provide an accurate and safe measurement of hepatic triglyceride content by measuring protons in the acyl groups of liver tissue triglycerides. The results of MRS were found to correlate well with histomorphometric analysis of liver tissue samples obtained with liver biopsy.[66-68] MRS is a promising technique that can help in the assessment and monitoring of patients with NAFLD undergoing therapy.

Focal forms of hepatic steatosis can represent a diagnostic challenge. Both focal fatty sparing and focal steatosis can be mistaken for hepatic tumor or metastatic disease on ultrasound or CT.[69] Focal fatty sparing may develop in areas with decreased portal blood flow receiving less fatty acids and triglycerides. The less commonly areas of focal steatosis may be explained by increased portal blood insulin level or the paucity of portal blood supply. Several radiologic features can help differentiate focal fatty sparing and focal steatosis from hepatic tumors (Table).[57,70]

In the future, other diagnostic modalities may be proved to provide a noninvasive way to diagnose NAFLD and differentiate NASH from simple steatosis. A recent study has suggested that contrast-enhanced ultrasonography can differentiate subjects with NASH from patients with fatty liver or other forms of chronic liver disease.[71] The authors used a contrast agent composed of inner gas and outer shell which was injected

Table. Radiologic features that can help differentiate focal fatty sparing and focal steatosis from hepatic tumors

Periligamentous and periportal location
Absence of vascular displacement or distortion
Absence of mass effect
Nonsherical shape
Angular or wedge-shaped margins
Lobar or segmental distribution

intravenously. Rapid disappearance of the microbubbles was noticed in patients with NASH compared to those with steatosis and hepatitis C, possibly due to decreased phagocytic power of Kupffer cells.

Liver stiffness measured by FibroScan (FS) has been proposed as a noninvasive tool to assess fibrosis and/or cirrhosis in patients with NAFLD. Stiffness may be explained by hepatocyte swelling, cholestasis, or infiltrates of inflammatory cells in the inflamed liver. However, liver stiffness measurement by FS may be quite difficult in obese subjects.[72]

Natural history

The progression of NAFLD in adult patients was seen in 26% to 37% of patients with NASH over a median follow-up period ranging from 3.2 to 5.6 years.[73-76] Progression to cirrhosis was documented in 9% of the patients in 2 studies.[73,74] The risk factors independently associated with progression were diabetes and presence of fibrosis in the initial biopsy. On the other hand, in adult patients with simple steatosis progression to NASH happens at a slow rate[74] but the exact proportion of the patients who will progress remains to be determined.

It is difficult to determine the natural history of NAFLD in children in the absence of long-term prospective studies. A recently published study[16] reported that 18 children had a follow-up biopsy over an average period of 28 months. No change was seen in 8 patients while 7 patients had progression of fibrosis, 3 patients had regression or disappearance of fibrosis following losing weight. The only patient who progressed from stage I fibrosis to cirrhosis had a significant weight gain over a short period of time.

Hepatocellular carcinoma (HCC) is a known complication of liver cirrhosis and can be seen in patients with NAFLD-associated cirrhosis.[77] Therefore, it is recommended to screen patients with NAFLD who develop cirrhosis for HCC periodically by ultrasound and serum alpha fetoprotein.

In patients with end-stage liver disease, orthotopic liver transplantation may be the only remaining consideration. Survival rates after liver transplant for patients with NAFLD-associated cirrhosis is not different from results following transplant due to other forms of liver disease.[78,79] Unfortunately NAFLD commonly recurs following transplant and can be severe enough to cause the failure of allograft.[79]

Predictors of advanced liver disease

Several factors have been investigated as possible predictors of the development of advanced liver disease in patients with NAFLD. In adults proposed predictors of fibrosis and cirrhosis included degree of obesity, diabetes mellitus type 2, older age, elevated ALT level, AST/ALT ratio greater than 0.8, hypertension, hypertriglyceridemia, high insulin resistance index and the grade of inflammation.[80,81]

In a recently published report, children with stage 3 or 4 portal fibrosis were found to be younger and have higher ALT levels. Children with no or mild fibrosis also had significantly less fat on biopsy than patients with moderate to severe portal fibrosis.[16]

These risk factors can help determine the most suitable candidates considered to undergo liver biopsy in order to target patients who are more likely to show features of advanced liver disease.

Treatment

NAFLD is not always a benign disorder in the pediatric age group. Advanced liver fibrosis and cirrhosis have been reported in children,[27] emphasizing the importance of early intervention to prevent long-term sequelae. Several therapeutic modalities targeting the presumed pathogenesis mechanisms in the development of NAFLD have been investigated.

Weight loss through nutritional counseling and exercise is the most reasonable initial management of patients with NAFLD. Weight reduction can lead to loss of adipose tissue which will reduce insulin resistance. Exercise improves muscular insulin sensitivity and leads to weight loss.[82] Reduction of body weight through dieting with or without exercise has been shown to improve liver enzymes in children and adults presumed to have NAFLD.[83,84] Other studies reported histological improvement.[85-87]

Decreasing caloric intake by cutting down on carbohydrate and saturated fat intake in addition to exercising for at least 30 minutes 3 times per week is recommended. A reasonable weight loss not exceeding 1.6 kg/week is advised as the patients who had more rapid weight loss developed portal inflammation and fibrosis.[85]

Antiobesity medications have also been tried. Orlistat, an enteric lipase inhibitor, has been shown to reduce weight, decrease liver enzymes and improve histological features when used for 6 months in a small group of patients with NAFLD.[88] Orlistat effects were also compared to sibutramine (a serotonin and norepinephrine reuptake inhibitor). In both groups, reduction of body mass index, improvement of insulin sensitivity, and improvement of biochemical and histological features were reported.[89] However the long-term effects of these medications on NAFLD remain to be determined.

Insulin resistance (IR), defined as impaired metabolic clearance of glucose, is known to play a central role in the genesis of fatty liver as well as NASH.[5] NAFLD is considered the hepatic manifestation of metabolic syndrome since the majority of NAFLD patients meet the criteria for metabolic syndrome. Therefore, insulin sensitizers have been the subject of intensive research efforts.

Thiazolidinediones is a group of drugs known to decrease insulin resistance mainly in adipose tissue by activating the nuclear transcription factor, peroxisome proliferators-activated receptor-γ (PRAPγ), by binding selective ligands.[90] The first drug, troglitazone, showed promising therapeutic effects in patients with NAFLD.[91] However, it was withdrawn from the market due to severe idiosyncratic hepatotoxicity. The second generation drugs, rosiglitazone and pioglitazone, have been shown to improve insulin sensitivity, liver enzymes and histological features in adult NAFLD patients.[92,93] However, the optimum dose and the duration of therapy have not been determined. The effects also seem to depend on continuing therapy as rebound increase of liver enzymes and worsening of histological features happen following cessation of therapy. Other concerns include increased body weight (though nonvisceral in distribution) and hepatotoxicity. At the time being, the use of these drugs should be limited to patients enrolled in studies.

Meformin is an insulin sensitizer which has been studied in children and adults with NAFLD.[94-98] The use of metformin has been associated with improved insulin sensitivity, liver enzymes and histological features. The beneficial effects are not associated with weight gain or hepatotoxicity as with thiazolidinediones. Metformin has also been shown to decrease the incidence of diabetes by 31% compared to placebo in a large trial of the Diabetes Prevention Program involving nondiabetics and prediabetics.[99] Taking into consideration that the majority of patients with NAFLD are either diabetics or prediabetics, the use of metformin seems to be a reasonable choice in these patients.

Oxidative stress has been implicated in the pathogenesis of NAFLD[98] and therefore antioxidants have been proposed as possible therapeutic options. Therefore, vitamin E alone or in combination with other medications or life-style modification has been evaluated for the treatment of NAFLD. In a small open-label trial, vitamin E was found to improve liver enzymes in 10 children with NAFLD. The enzymes however increased after cessation of therapy.[100] In another randomized trial vitamin E was superior to placebo in a study involving 28 children.[101] Similarly, vitamin E alone or in combination with other medications or life-style modification has been evaluated in adults with NAFLD with conflicting results.[102,103] Although vitamin E is inexpensive and well-tolerated, the lack of proved efficacy and the concern about long-term safety do not support its use in patients with NAFLD.

Dyslipidemia is common among patients with NAFLD. Although the specific pathways leading to inflammation and fibrosis in patients with NAFLD are not clearly delineated, evidence supports a role for dysregulated lipid partitioning mediated by insulin resistance and concomitant altered cytokine profiles.[104] Therefore, several antihyperlipidemic agents including statins, gemfibrozil, probucol and omega 3 fatty acids have been evaluated in the therapy of adult patients with NAFLD.[105-110] However, in the absence of randomized trials, including histological follow-up, the efficacy of this approach remains uncertain. Antihyperlipidemic agents may have a role in patients with significant dyslipidemia and increased risk for cardiovascular disorders.

Ursodeoxycholic acid is a known chloretic, immunomodulator and cytoprotective agent. Despite initial enthusiasm following a report of the effects of UDCA in patients with NAFLD,[111] the effects could not be reproduced in a large randomized placebo-controlled trial involving 166 patients with NASH for a duration of 2 years.[112]

The search for a perfect therapy for NAFLD continues. Ideally such therapy should be safe, effective, well-tolerated, of limited duration and the effects should be sustained after cessation of treatment. Promising agents undergoing research include angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), probiotics, antibiotics, lactulose and nateglinide (insulin secretagogue). At the time being and in the absence of a proved effective pharmacologic therapy in the pediatric age group, diet and exercise aiming at reasonable weight loss remains to be the safest approach.

Surgery

The National Institute of Health Consensus Conference has recommended that surgical treatment of obesity should be considered in patients with BMI greater than 40 or in patients with BMI than 35 and with obesity-associated health disorders.[113] However, the safety and effects of this approach has not been examined in children.

Several obesity surgical procedures have been described. The first tried procedure was jejunoileal bypass in which the proximal jejunum is anastomosed to the ileum leaving a long excluded segment. Other surgical options include biliopancreatic diversion,

gastroplasty with stapling, and gastric banding.[114]

The most effective and safest antiobesity surgical procedure is gastric bypass.[115-117] It has been successfully performed in patients with cirrhosis[118] or after liver transplant due to recurrent NASH.[119] Marked improvement in steatosis, inflammation, ballooning degeneration and perisinusoidal fibrosis have been reported following gastric bypass. However, there was little improvement in periportal fibrosis.[120]

However, the antiobesity procedures are not without risks and despite low mortality rate it can be associated with significant morbidity including pulmonary embolism, sepsis, wound infection, volvulus, nutrient deficiencies, stomal stenosis, dilatation, ulceration and bleeding.[116,121] Approximately one third of the patients develop gallstones within six months of the procedure and 10% of the patients develop symptoms requiring cholecystectomy. However, the use of UDCA can dramatically decrease the incidence of gallstones development.[122]

Finally, NAFLD affects a substantial portion of the population including children. The rising incidence of NAFLD, NASH and cirrhosis emphasizes the need for effective treatment options. However, despite the tremendous gain in our understanding and the major strides we have made over the last 2 decades, lack of complete understanding of the pathogenesis of NAFLD still limits our ability to develop novel therapeutic modalities that can target the metabolic derangements implicated in the development of the disorder. Because of the high prevalence and the consequences of the disease, we emphasize the importance of increased awareness and screening for NAFLD by noninvasive methods especially in high risk groups. Prevention, early recognition and management of obesity especially in the pediatric age group by adopting healthy diet and life-style may prevent the development of NAFLD and its progression to advanced liver disease.

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