Evolution of NAFLD and Its Management

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Review Article

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Introduction

Introduction

- NAFLD: one of the most common causes of chronic liver disease
- Global prevalence ~25%
- Highest prevalence in Middle East (32%)
- Increased in adolescent patients (3-18%)

Introduction

- Progressive disease w/ significant complications
- Cirrhosis, Hepatocellular Carcinoma, Increased mortality
- Rapidly becoming the most common indication for liver transplant
- Annual direct medical costs exceed $100 billion in the United States

Phenotypes

Phenotypes

- A continuum of liver conditions
- Ranging from steatosis (fatty liver) to NASH, steatohepatitis w/ fibrosis and cirrhosis
- Can result in liver injury in the absence of other liver disease etiologies e.g. medications, viral hepatitis and alcohol

Phenotypes

- Often suspected in the setting of the presence of other metabolic comorbidities
- Detected incidentally through noninvasive imaging
- Up to 78% of patients with NAFLD may have normal liver enzymes

Phenotypes

- Fatty liver is defined as >5% steatosis
- US or CT can reliably detect steatosis when it comprises >20% of liver mass
- MRI can detect as little as 5% steatosis

Phenotypes

- **NASH** is associated with:
- steatosis,
- Lobular and portal inflammation,
- Hepatocyte damage in the form of hepatocyte ballooning, and
- Pericellular fibrosis that can progress to liver cirrhosis

Phenotypes

- NASH is typically suspected in :
- Patients with fatty liver and abnormal aminotransferases
- However, it can only be diagnosed with liver biopsy

Risk Factors and Pathogenesis

Risk Factors and Pathogenesis

- NAFLD is a manifestation of
- Metabolic syndrome, with insulin resistance perhaps being the common pathogenic event
- Weight gain and the presence of Metabolic syndrome remain the strongest risk factors

Risk Factors and Pathogenesis

- Zelber-Sagi et al followed 147 patients who had no ultrasound evidence of NAFLD at baseline for 7 years and reported that 28 (19%) developed NAFLD
- Metabolic syndrome was 4 times more prevalent at baseline in patients who developed NALFD

Risk Factors and Pathogenesis

- Additionally,
- Baseline fasting hyperinsulinemia, defined as insulin > 25 µU/mL,
- was 5 times more prevalent in those who developed NAFLD

Risk Factors and Pathogenesis

- Multiple studies noted that NASH is:
- more prevalent and progressive in the setting of insulin resistance and
- Diabetes mellitus (DM),
- with DM being an independent predictor of moderate to severe fibrosis

Risk Factors and Pathogenesis

- Donnelly et al reported that:
- 59% ± 9.9% of triglycerides in the liver were originally released from adipose tissue,
- 26.1% ± 6.7% were from de novo lipogenesis, and
- 14.9% ± 7% were from dietary sources

Risk Factors and Pathogenesis

- As the delivery of these energy substrates exceeds the liver's capacity to handle them,
- the triglyceride storage pool continues to grow
- Metabolites of these FFA cause hepatocellular injury

Risk Factors and Pathogenesis

- Endoplasmic reticulum (ER) stress,
- Apoptosis,
- Inflammation,
- Necrosis, and
- Dysmorphic features such as ballooning and Mallory-Denk body formation.

Risk Factors and Pathogenesis

- Although this progression from fatty liver and steatosis to NASH makes sense, it does not occur in all patients
- 41% of patients with NASH experience progression of fibrosis,
- and up to 25% can progress to cirrhosis

Risk Factors and Pathogenesis

- A study noted that consumption of fructose was nearly 2-fold to 3-fold higher in patients with NAFLD

Risk Factors and Pathogenesis

- Kechagias et al: eating at least 2 fast-food meals per day and not exceeding physical activity of 5000 steps per day over 4 weeks
- Over this short period, average body weight increased from 67.6 ± 9.1 kg to 74 ± 11 kg
- Serum ALT increased from 22.1 ± 11.4 U/L to 97 ± 103 U/L (range of 19.4–447 U/L)

Risk Factors and Pathogenesis

- Red meat, Trans fat, High-fructose corn syrup, highly refined Carbohydrates, Low Fiber, and High energy density often found in Fast Food,
- combined with Sedentary behavior,
- leads to Caloric excess, Weight gain, and Insulin resistance,
- leads to the development of Hepatoxicity

Risk Factors and Pathogenesis

- Once NAFLD progresses to inflammation, fibrosis, and cirrhosis,
- patients must be monitored for secondary risks and complications, including those associated with
- portal hypertension (ascites, variceal bleeding), end-stage liver disease, and HCC

Risk Factors and Pathogenesis

- Development of advanced fibrosis :
- increases the risk of HCC by >25-fold
- In NAFLD with 12 years of follow-up, HCC cumulative rate was 0.5%
- In NASH, the 5-year cumulative incidence rate was as high as 7.6%

Risk Factors and Pathogenesis

- Associated with a number of metabolic diseases
- Younossi et al: a meta-analysis of 86 studies reported high prevalence of
- metabolic comorbidities in patients with NAFLD, including
- Obesity (51.3%), Type 2 Diabetes (22.5%), Hyperlipidemia (69.2%),
- Hypertension (39.3%), and Metabolic syndrome (42.5%)

Risk Factors and Pathogenesis

- The leading cause of death in these patients were cardiovascular events followed by
- Non-hepatic malignancy
- Liver-related death was the third most common cause

Risk Factors and Pathogenesis

- Fibrosis may be a key predictor of overall mortality,
- As 2 studies have noted :
- Increased mortality irrespective of the presence of steatohepatitis

Treatment Options

Treatment Options

- Currently, there are no specific medications that directly treat NAFLD
- The primary focus of treatment has been to:
- Lose weight and improve insulin resistance through
- lifestyle, medications, or endoscopic/surgical intervention

EFFICACY

RISK

LIFESTYLE MODIFICATIONS

Avoidance of a diet rich in:
- Red meat
- Trans fats
- High-fructose corn syrup
- Highly refined carbohydrates
- Low fiber
- High energy density

Dietary intervention:
- Calorie deficit of 500–1000 Cals/day

Exercise:
- 30–60 minutes of moderate intestity activity
- 3–4 times/week

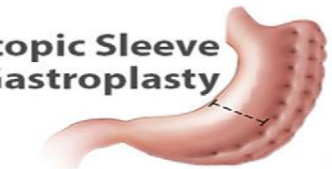
Particular interventions:
- Carbohydrate restriction
- Mediterranean diet

MEDICATIONS AND SUPPLEMENTS

- Metformin
- (TZDs)
- (GLP-1)
- (SGLT2)
- Statins
- Fish oil
- Orlistat

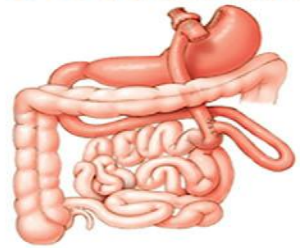
ENDOSCOPIC THERAPY

Intragastric Balloon

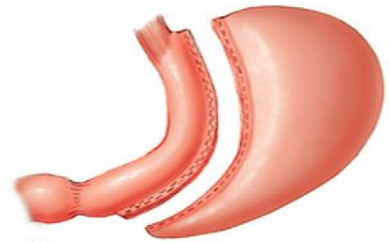


Endoscopic Sleeve Gastroplasty

BARIATRIC SURGERY



Roux-en-Y Gastric Bypass



Sleeve Gastrectomy

Treatment Options: Lifestyle interventions

- Studies have taken similar approaches to dietary interventions by either
- aiming for a caloric deficit of 300–1000 kcal/d or creating an overall calorie target for the day (1200–1800 kcal/d or 20–30 kcal/kg/d)
- Many studies have added a component of moderate-intensity activity 3–4 times per week for 30–60 minutes per episode

Treatment Options: Lifestyle interventions

- these interventions lead to a weight loss of −3.61 kg
- Although modest, resulted in significant improvement in blood tests, including a reduction of
- ALT (−9.81 U/L), AST (−4.84 U/L), alkaline phosphatase (−5.53 U/L), and GGT (−4.35 U/L)
- were also associated with improvements in liver steatosis and liver stiffness
- Despite this, the meta-analysis did not find evidence of histological changes in inflammation, ballooning, or fibrosis

Treatment Options: Lifestyle interventions

- The degree of weight loss was independently associated with improvement in NASH related histological features:
- 58%of patients who lost >5% body weight had resolution of NASH,
- whereas 90% of patients who lost >=10% body weight had resolution of NASH

Treatment Options: Lifestyle interventions

- A short-term (2 weeks) study in 18 obese pts with NAFLD compared a calorie-restricted diet (1200–1500 kcal/d) vs a carbohydrate-restricted diet (<20 g/d)
- Weight loss was similar in both groups and resulted in improvements in liver triglyceride levels and AST
- However, the reduction in liver triglycerides was significantly more in the carbohydrate-restricted diet (−55% ± 14%) compared with the calorie-restriction group (−28% ± 23%)

Treatment Options: Lifestyle interventions

- A study in obese patients with diabetes examined the impact on liver studies of 3 different diets:
- the American Diabetes Association diet, low-glycemic-index diet, and the Mediterranean diet
- They noted that the decrease in ALT was the most significant in participants on the Mediterranean diet

Treatment Options: Lifestyle interventions

- Mediterranean diet also resulted in greater reduction in
- hepatic steatosis compared with the control diet
- Insulin sensitivity improved with the Mediterranean diet,
- whereas there was no change with the control diet

Treatment Options: Medications

- Currently, there are no specific pharmacological treatments with proven efficacy for NAFLD
- So treatment focuses on coexisting conditions like
- diabetes, fat disorders, and obesity/weight loss in order to
- reduce insulin resistance and improve liver function

Medications: Metformin

- Currently the recommended first-line agent for the management of diabetes
- Marchesini et al reported on 20 consecutive patients who presented with NAFLD (steatosis on ultrasound and elevation in ALT)
- treated with metformin 500 mg 3 times per day
- Mean ALT levels decreased by 50% at 4 months, and liver size decreased by 20%

Medications: Metformin

- Bugianesi et al randomized 110 adults with NAFLD to:
- either metformin at a maximum dose of 2000 mg/d
- or vitamin E 400 IU/d along with dietary counseling (calorie deficit of 500 kcal/wk)
- They found that aminotransferase levels improved in all groups,
- although the effect in the metformin group was larger, with ALT levels normalizing in 56% of cases

Medications: Metformin

- Although extremely rare, cases of hepatotoxicity with metformin use have been reported
- Despite these, systemic reviews have not found that metformin exacerbates liver injury and
- may have some beneficial effect in patients with NAFLD
- Thus NAFLD or abnormal transaminase levels should not be considered a contraindication to metformin use
- Instead, patients with severe hepatic insufficiency should avoid metformin because of increased risk of developing lactic acidosis

Medications: Thiazolidinediones

- tremendous potential in patients with NAFLD because they:
- promote preadipocyte differentiation into adipocytes and
- may induce a redistribution of fat from visceral sites such as liver and muscle to peripheral subcutaneous adipose tissue,
- increase circulating adiponectin levels, and
- improve insulin sensitivity

Medications: Thiazolidinediones

- In 30 biopsy-proven cases of NASH,
- use of rosiglitazone showed improvement in
- hepatic steatosis, inflammation, ballooning, and perisinusoidal fibrosis
- As expected, weight gain occurred in 67% of patients (median weight gain was 7.3%)

Medications: Thiazolidinediones

- There was improvement in ALT and liver steatosis;
- however, there was no change in ballooning or fibrosis over the 3-year period
- Trials using pioglitazone have shown similar mixed results
- Because of these results, additional studies have focused more on patients with NAFLD
- who are at risk for diabetes or have diabetes

Medications: GLP-1 analogues

- Have potential in patients with NAFLD because
- they induce glucose-mediated insulin secretion,
- reduce glucagon secretion, and also
- decrease gastric emptying and
- suppress appetite, promoting weight loss

Medications: GLP-1 analogues

- Armstrong et al randomized 52 adults with histologically confirmed NASH
- to either liraglutide or placebo
- Over 48 weeks of follow-up,
- 39% of patients in the liraglutide group had resolution of NAFLD, compared with 9% of the placebo group
- The liraglutide group also had less progression of fibrosis (9% vs 36% in the placebo group).

Medications: SGLT2 inhibitors

- By inhibiting SGLT-2, these agents decrease renal reabsorption of glucose and increase its excretion
- Despite this unique mechanism, animal studies have shown that in addition to improving glycemic control,
- SGLT-2 inhibitors also decrease hepatic fat perhaps through increase in glucagon levels

Medications: SGLT2 inhibitors

- A recent meta-analysis noted that 8 studies, including a total of 214 patients, had evaluated the impact of SGLT- 2 inhibitors on NAFLD:
- All studies noted a significant improvement in AST and ALT
- Some studies also noted that this improvement exceeded or matched that of other diabetes medications
- such as metformin, pioglitazone, or sitagliptin

Medications: SGLT2 inhibitors

- Also 5 studies have evaluated the impact of SGLT-2 inhibitors on hepatic fat and
- noted significant improvement:
- The use of SGLT-2 inhibitors also lead to a decrease in liver fibrosis in multiple trials

Medications: Statins

- Concern for hepatotoxicity has limited their use in patients with preexisting liver disease such as those with NAFLD
- Despite this concern, data from animal and human studies have revealed
- benefit in both preventing the development and progression of NAFLD and leading to improvements in liver steatosis and fibrosis

Medications: Statins

- In a large trial that randomized 1005 participants to a daily combination of:
- atorvastatin 20 mg, vitamin C 1000 mg, and vitamin E 1000 IU vs placebo,
- participants had NAFLD at baseline
- At the end of the follow-up period, significantly more participants in the treatment group had resolution of NAFLD compared with those in the placebo group
- In those without NAFLD, 17.6% of the placebo group developed NAFLD compared with 12.1% of those in the treatment group

Medications: Orlistat

- A reversible inhibitor of gastric and pancreatic lipases
- that results in a reduction in absorption of ~30% of dietary fat
- efficacy in producing weight loss, preventing the development of DM,
- and also in improving glycemic control in those with DM

Medications: Orlistat

- Harrison et al randomized 50 overweight patients to receive orlistat (120 mg 3 times per day) or placebo in addition to 1400 kcal/d diet plus vitamin E (800 IU/d)
- Patients underwent liver biopsies at baseline and at 36 weeks
- There was no significant difference in weight loss between the groups,
- both groups had similar improvement in aminotransferases, hepatic steatosis, inflammation, ballooning, and NAFLD scores

Medications: Vitamins and Supplements

- Supplementation with fish oil has been particularly explored,
- as there are emerging data that individuals with NAFLD tend to have lower fish consumption and
- higher ω-6 to ω-3 fatty acid consumption compared with controls
- Additionally, in patients with NAFLD, hepatic long-chain fatty acids also tend to have lower composition of ω-3 PUFAs and higher ω-6:ω-3 PUFA ratios

Medications: Vitamins and Supplements

- A recent meta-analysis of 9 studies (355 participants) noted that
- supplementation with ω-3 PUFA or fish oil resulted in
- improvement in liver fat and AST,
- although a great deal of heterogeneity was noted

Medications: Vitamins and Supplements

- The use of vitamin E has been explored in NAFLD, given that
- one of the pathogenic mechanisms is steatosis-induced fat peroxidation,
- which tends to consume antioxidant enzymes.

Medications: Vitamins and Supplements

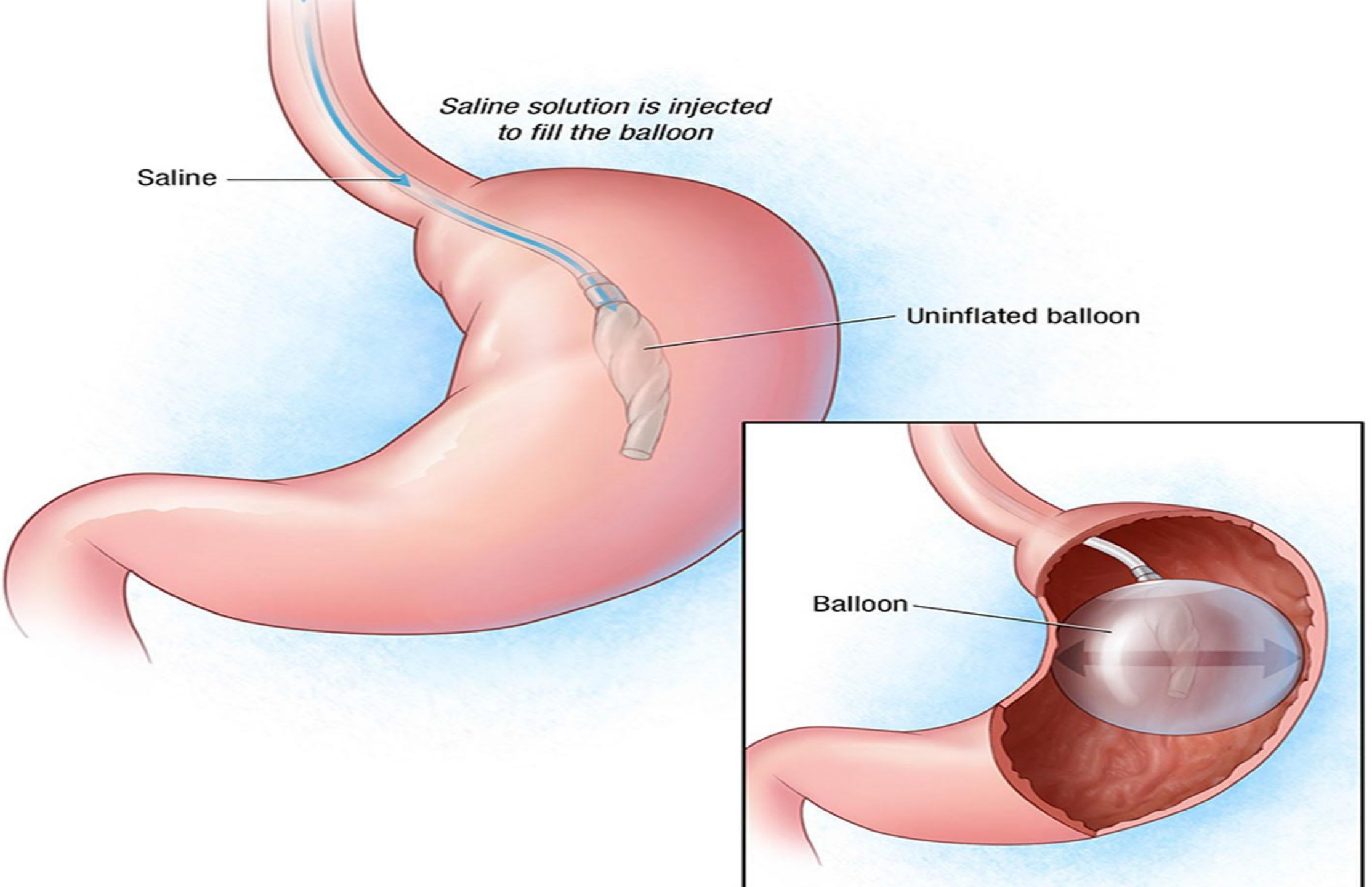
- Two trials compared the efficacy of vitamin E vs metformin in both adults and pediatric population
- In both studies, they noted that although the vitamin E group did have improvement in aminotransferases, this improvement was not superior to metformin
- Therefore, from the data available, it is difficult to ascertain whether vitamin E provides added benefit above that of weight loss or one that is superior to other medications such as metformin.

Endoscopic Procedures

- endoscopic therapeutic procedures have emerged as a weight loss option for individuals
- who have been unsuccessful in losing and sustaining weight loss with lifestyle interventions
- or medications and
- also do not wish to undergo bariatric surgery

Endoscopic Procedures

- there are 2 major approaches to endoscopic bariatric therapies:
- restrictive and malabsorptive
- The duodeno-jejunal bypass sleeve (DJBS) is an example of malabsorptive therapy,
- whereas the restrictive procedures include adjustable intragastric balloons (IGBs),
- endoscopic sleeve gastroplasty (ESG),
- trans-oral gastroplasty, and
- trans-oral endoscopic restrictive implant system

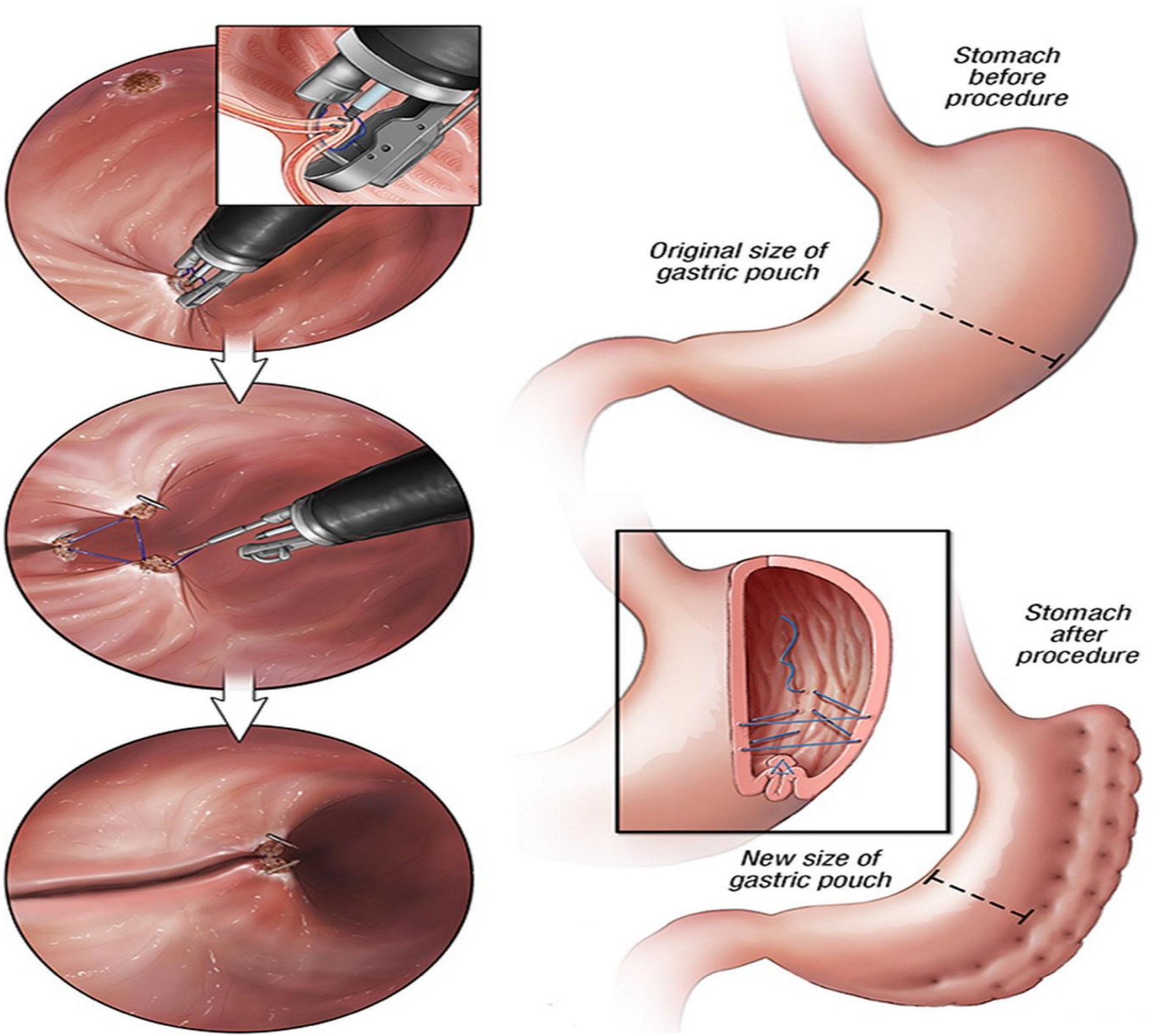

Saline solution is injected
to fill the balloon
Saline
Uninflated balloon
Balloon

Endoscopic Procedures

- Lee et al conducted a pilot study in which 18 patients with histological evidence of NASH were randomized
- to either IGB or sham procedure
- Both groups also instructed to follow a diet of 1200–1500 calories/d as well as target daily exercise
- There was a great decrease in BMI and NAFLD activity score and a trend toward improvement in steatosis in the IGB group
- No significant change in inflammation, ballooning, or fibrosis was noted

Endoscopic Procedures

- ESG works by reducing the effective gastric volume by suturing the walls of stomach together, a process known as plication
- Trans-oral gastroplasty works in the same way, except it usually uses the newer endoscopic stapler device rather than the suturing device
- Similar to IGB, both of these procedures can be done in an ambulatory setting.


Stomach
before
procedure
Original size of
gastric pouch
Stomach
after
procedure
New size of
gastric pouch

Endoscopic Procedures

- Rosenblatt et al evaluated the impact of ESG in 48 obese individuals
- In just 6 weeks, ALT decreased from 30 to 21, whereas AST decreased from 24 to 21
- Liver steatosis index also improved significantly (50.5 to 42.6) in that time as well

Endoscopic Procedures

- Another promising endoscopic intervention is the DJBS,
- which is an endoscopically delivered device that has a self-expanding basket that seats in the duodenal bulb and a long sheath that bypasses the proximal small intestine (up to jejunum) from absorbing food
- De Jonge et al explored the impact of DJBS in 17 obese individuals with type 2 diabetes who had received the DJBS for 24 weeks
- Levels of AST, ALT, and GGT were significantly reduced and remained so in those with 6 months of follow-up

Bariatric Surgery

- Bariatric surgery still remains one of the most effective and successful method of producing sustained weight loss for obese patients
- These procedures lead to weight reduction by either restricting the volume of food that can be consumed,
- creating malabsorption,
- or a combination of both

Bariatric Surgery

- Sleeve gastrectomy is rapidly becoming one of the most common restrictive procedures being performed
- A retrospective study of 84 obese individuals with ultrasound-confirmed NAFLD showed that
- 56% had complete resolution postoperatively

Bariatric Surgery

- Recently, a meta-analysis conducted on the impact of bariatric surgery on NAFLD found 32 studies including over 2649 biopsies performed at follow-up
- Mean weight loss was ~25%,
- and surgery resulted in resolution of steatosis in 66%,
- inflammation in 50%,
- ballooning degeneration in 76%, and
- fibrosis in 40%

Summary

Summary

- Obesity and its associated comorbidities such as NAFLD tax the healthcare resources of developed nations.
- These comorbidities are associated with significant complications
- it is imperative to diagnose them early and begin treatment focusing on weight loss and improvement in insulin sensitivity
- The foundation is lifestyle modification that begins with a
- reduction in the consumption of foods containing high amounts of red meat,
- trans fat, refined carbohydrates, and high fructose; are low fiber; and are high in energy density.

Summary

- a caloric deficit of 500–1000 calories/d and an increase in moderate-intensity activity are added.
- Often, an intense program that consists of weekly touch points is necessary to produce adequate weight loss.
- despite this intense program, not all patients respond, and additional therapeutic intervention is often needed.
- a number of medications approved for weight loss and DM have shown to be beneficial in patients with obesity.
- multiple endoscopic and bariatric options are also now available for patients who are unsuccessful with previous efforts.

What are your experiences in this field?