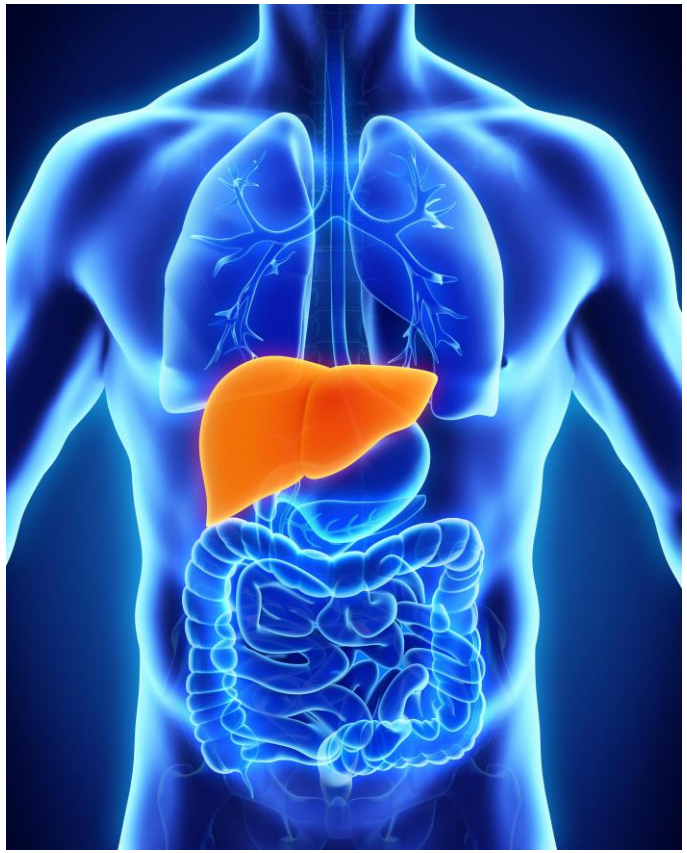
NAFLD – What We Need To Know

The prevalence of NAFLD is considerably higher than previously estimated and is continuing to rise

NAFLD is significantly higher among men than among women

Greater awareness of NAFLD and what it means to the health of the body is the first step to prevention

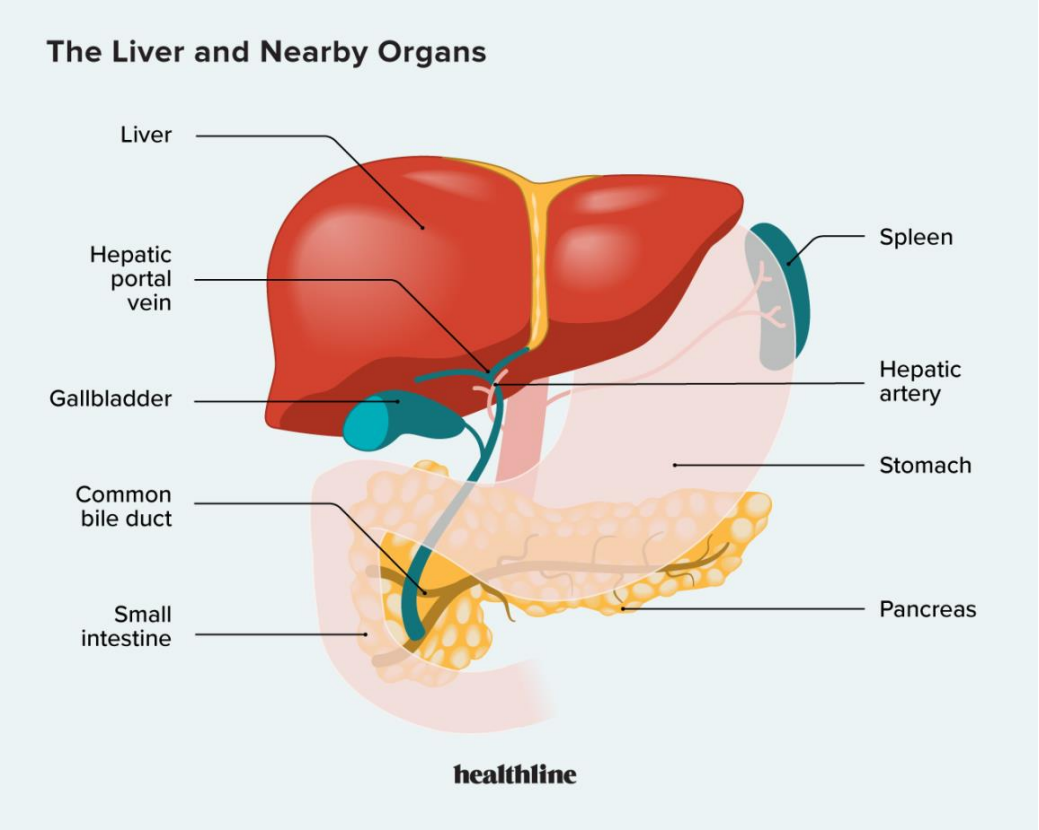


So why is it on the rise?

Two reasons:

1. The relationship of the liver to other areas in the body
2. The role of the gut in helping or hurting liver function

We can’t look at this condition as just a result of external factors – diet, alcohol etc.



What is NAFLD?

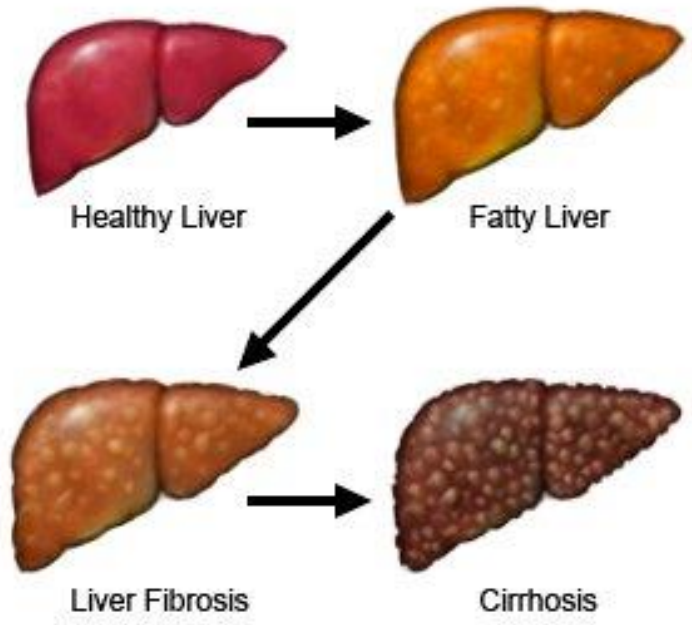
Non-Alcoholic Fatty Liver Disease

Occurs when there is too much fat in the liver in people who do not drink alcohol

Most often seen in those who are suffering from obesity or are overweight

Can lead to NASH (nonalcoholic steatohepatitis) where the liver swells and fat deposits in the liver

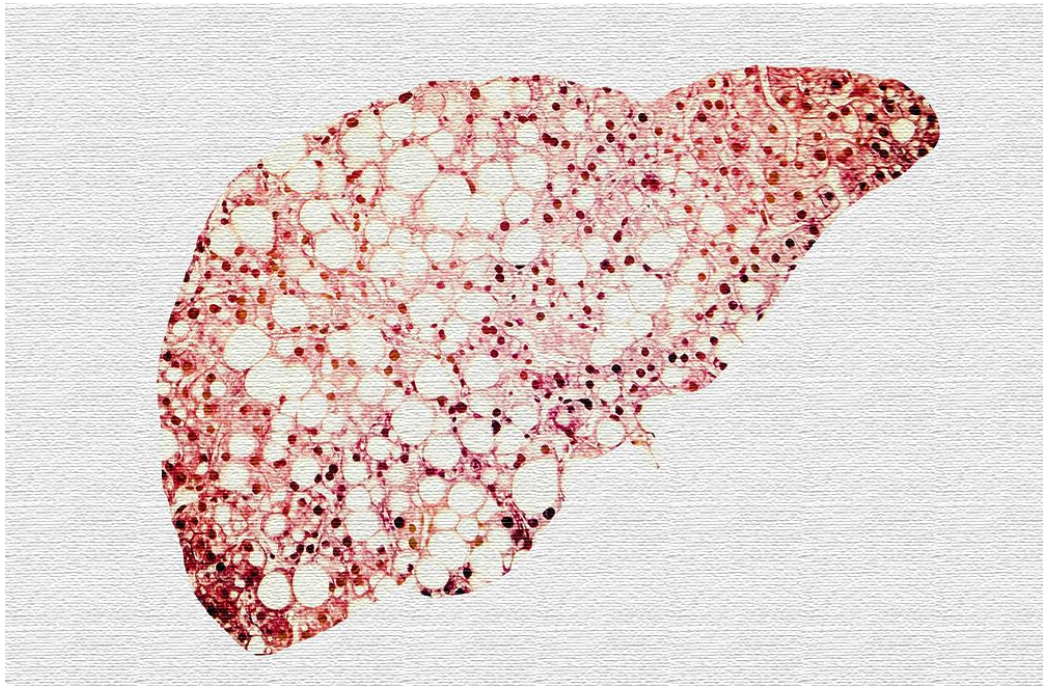
Can lead to scarring and cirrhosis and possibly liver cancer



Stages of Liver Damage

There’s a movement to change the name to metabolic dysfunction-associated steatotic liver disease (MASLD)

And NASH would become MASH (metabolic dysfunction-associated steatohepatitis)



There can be no symptoms but typical symptoms are:

Fatigue

Not feeling well

Pain or discomfort in the upper right belly area

Possible NASH and cirrhosis symptoms:

Itchy skin

Abdominal swelling, also called ascites

Shortness of breath

Swelling of the legs

Spider-like blood vessels just beneath the skin's surface

Enlarged spleen

Red palms

Yellowing of the skin and eyes, or jaundice

Conventional Factors

Genetics

Overweight or obesity

Insulin resistance

Type 2 diabetes

High Triglycerides

Underactive thyroid or pituitary

Sleep apnea

PCOS

Metabolic Syndrome

Dysbiosis

Complications

Ascites: Fluid buildup in the stomach area

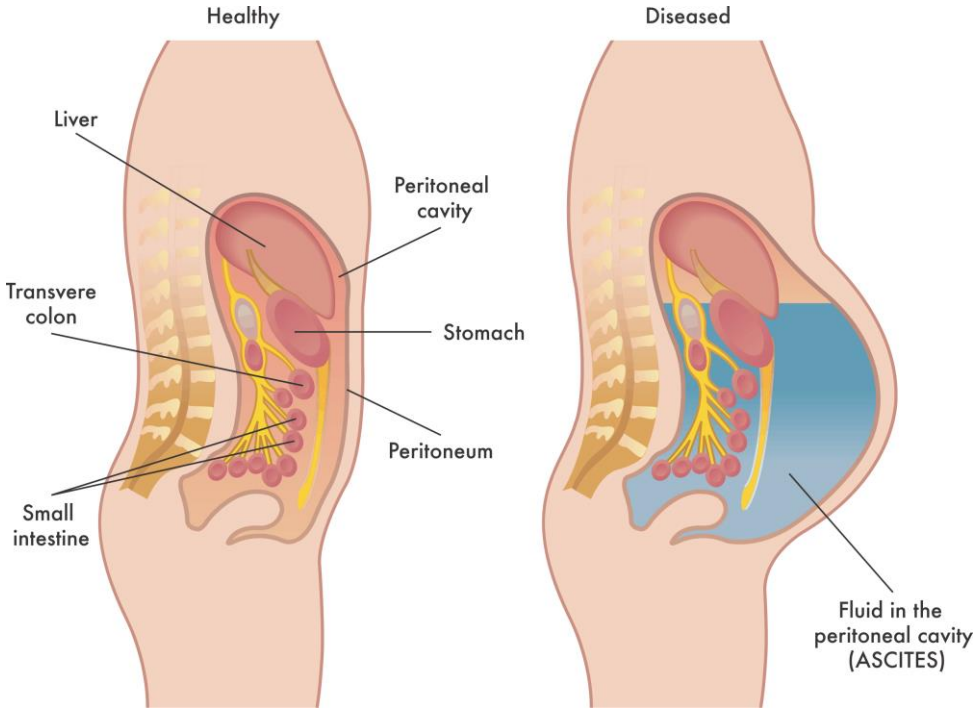
Swollen veins in the esophagus, or esophageal varices, which can rupture and bleed

Confusion, sleepiness and slurred speech, also called hepatic encephalopathy

Overactive spleen, which can lead to less blood platelets

Liver cancer

End-stage liver failure



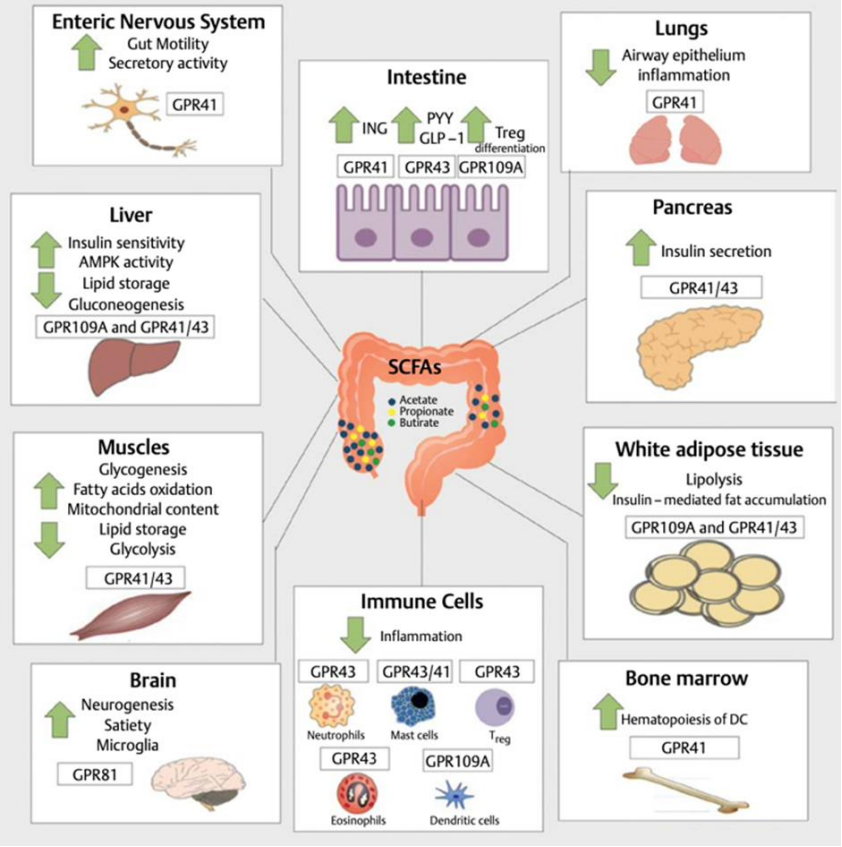
Biomarkers

Abnormalities in SCFAs, including butyrate, propionate, and acetate, are noted in NAFLD patients

SCFAs play roles in energy balance, anti-inflammation, and vasodilation. Dysregulation of SCFAs is linked to metabolic disturbances in NAFLD

Bile Acid Profile: Changes in bile acid composition due to dysbiosis can contribute to hepatic fat accumulation in NAFLD

Reflects the gut-liver axis



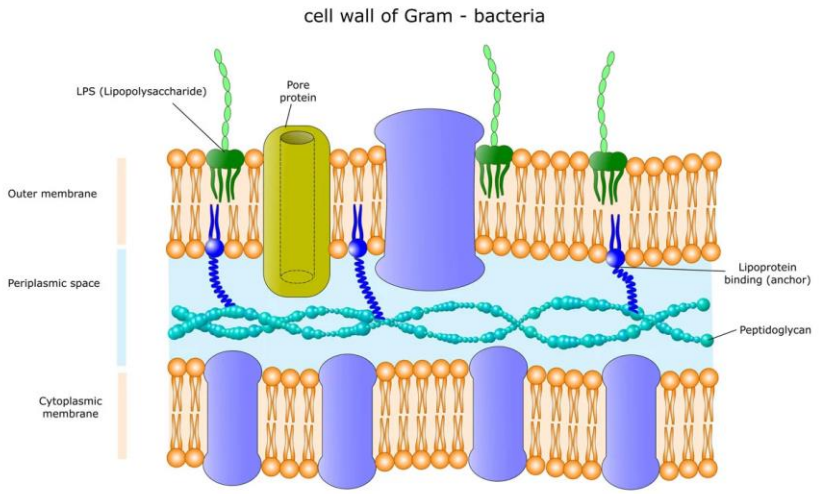
Inflammatory Markers: TNF-α, IL-1β, and IL-6, are elevated in NAFLD.

Dysbiosis triggers the release of pro-inflammatory cytokines via the gut-liver axis, contributing to low-grade inflammation, a hallmark of NAFLD.

The gut-liver axis communication through PRRs is central to the inflammatory cascade in NAFLD

Pattern Recognition Receptors - sensors that can be used for pathogen detection are produced by gut bacteria

Example is LPS locking on to the receptor and could be used as a biomarker



Understanding these biomarkers provides insights into the intricate relationship between gut microbiota and NAFLD offering potential avenues for diagnostic and therapeutic interventions

Monitoring these markers may help in assessing disease progression and developing targeted treatments for individuals with NAFLD

Drugs Use To Treat NAFLD

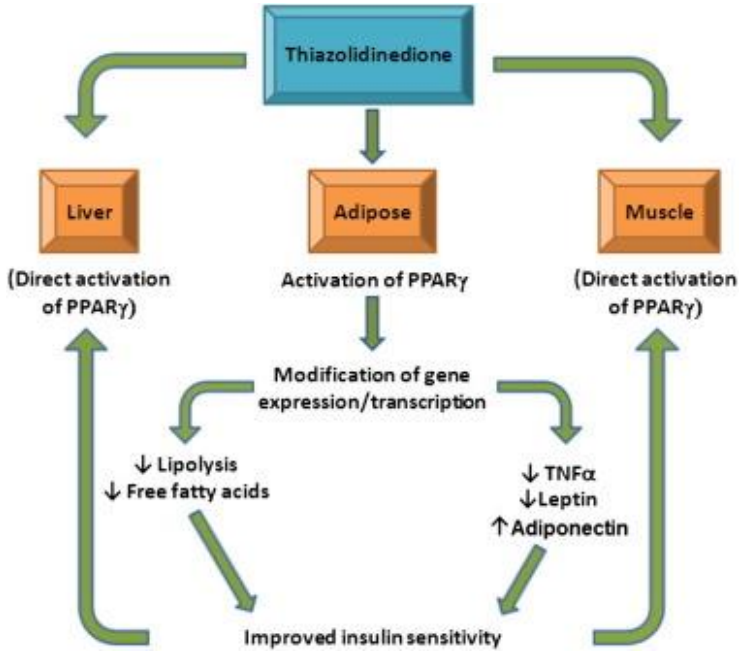
Insulin Sensitizers (Thiazolidinediones - TZDs): Increase insulin sensitivity.

Pioglitazone is better than rosiglitazone, which has restrictions

Considerations: Side effects include weight gain, edema, heart failure, and bone density reduction.

Antioxidants (Vitamin E): 800 IU/d

Considerations: Improves serum aminotransferase levels, hepatic steatosis, and lobular inflammation. Long-term safety concerns exist



Lipid-Lowering Drugs (Statins, Ezetimibe): Statins inhibit cholesterol synthesis; ezetimibe inhibits cholesterol absorption

Considerations: Statins have shown mixed results, with potential anti-inflammatory effects. Ezetimibe may improve liver histology but can increase hepatic long-chain fatty acids and hemoglobin A1c levels

Pentoxifylline: Nonselective phosphodiesterase(repairs DNA/RNA) inhibitor; inhibits TNF-α synthesis

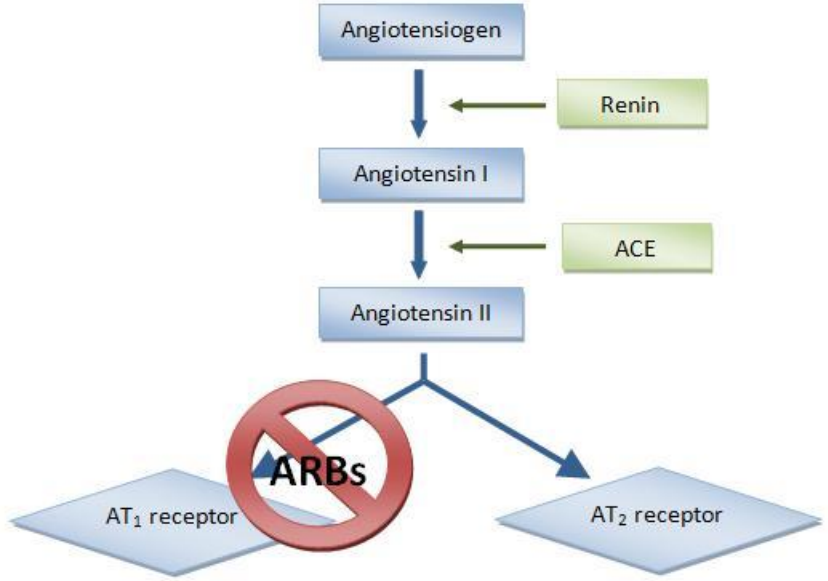
Considerations: Mixed results in trials. Some studies show improvement in serum aminotransferase levels while others report no significant benefits. Side effects include nausea and vomiting

Ursodeoxycholic Acid (UDCA): Hydrophilic bile acid with antiapoptotic properties

Considerations: Limited efficacy; not recommended by American guidelines for NAFLD/NASH

Angiotensin Receptor Blockers: Modulates insulin sensitivity; associated with the pathogenesis of NAFLD/NASH

Considerations: Telmisartan and valsartan have shown benefits in decreasing serum ALT levels, HOMA-IR (used to calculate insulin resistance), and NAS in NASH patients



Drugs that can contribute to NAFLD

The relationship between drugs and NAFLD can be complex.

It’s going to depend on other factors like diet and alcohol that a person consumes while taking drugs

Although acetaminophen is associated with liver damage – it is not a factor in NAFLD

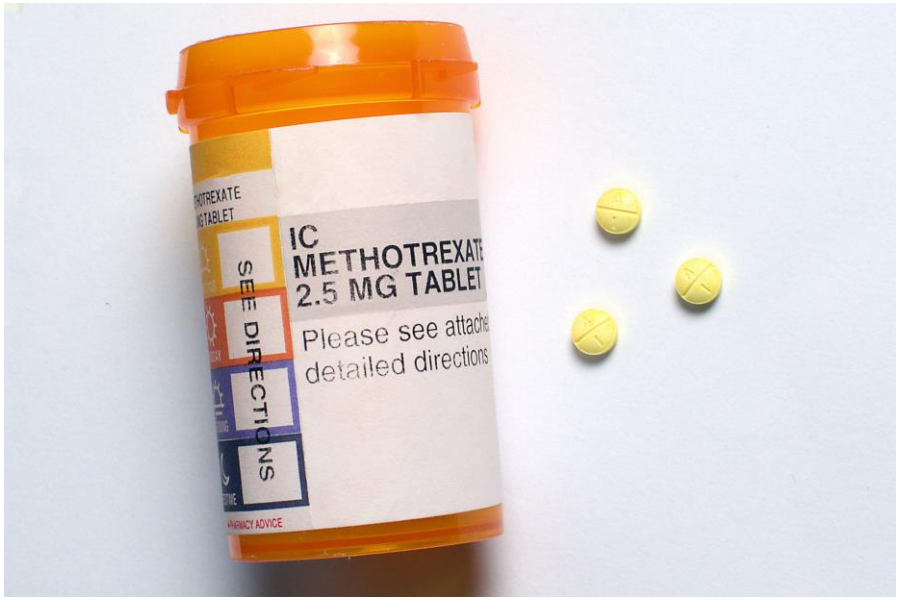
Two different types of damage

Acetaminophen should be used with caution by those with NAFLD

Drugs To Avoid

Amiodarone: This antiarrhythmic medication is used to treat irregular heartbeats. Amiodarone has been linked to the development of steatohepatitis, a more severe form of NAFLD

Methotrexate: This drug is commonly used to treat conditions like rheumatoid arthritis, psoriasis, and certain types of cancer. Long-term use of methotrexate has been associated with hepatic steatosis, and in some cases, it can progress to more severe liver disease

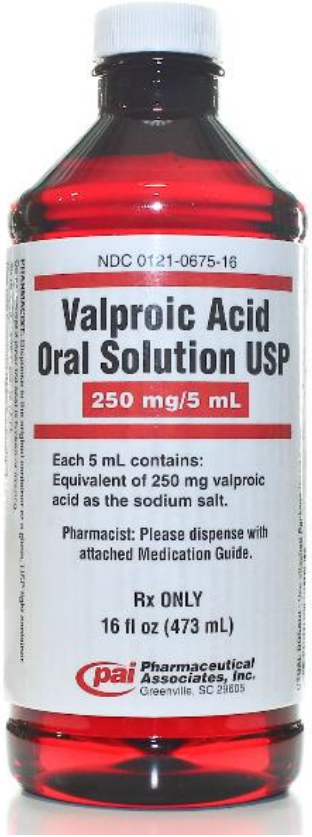


Tamoxifen: Used in the treatment of breast cancer, tamoxifen has been linked to fatty liver changes. The mechanism is not entirely clear, but it may be related to alterations in lipid metabolism

Glucocorticoids: Long-term use of systemic glucocorticoids, such as prednisone, can lead to fat accumulation in the liver and contribute to the development of NAFLD

Antiretroviral medications: Some drugs used in the treatment of HIV, particularly protease inhibitors, have been associated with metabolic abnormalities, including fat accumulation in the liver.

Valproic acid: This anticonvulsant medication is used to treat epilepsy and bipolar disorder. Prolonged use of valproic acid has been linked to hepatic steatosis.



Conventional Solution

Eat a diet high in fruits, vegetables, whole grains and healthy fats.

Limit alcohol, simple sugars (including pop)

Don’t overeat

Try to maintain a healthy weight

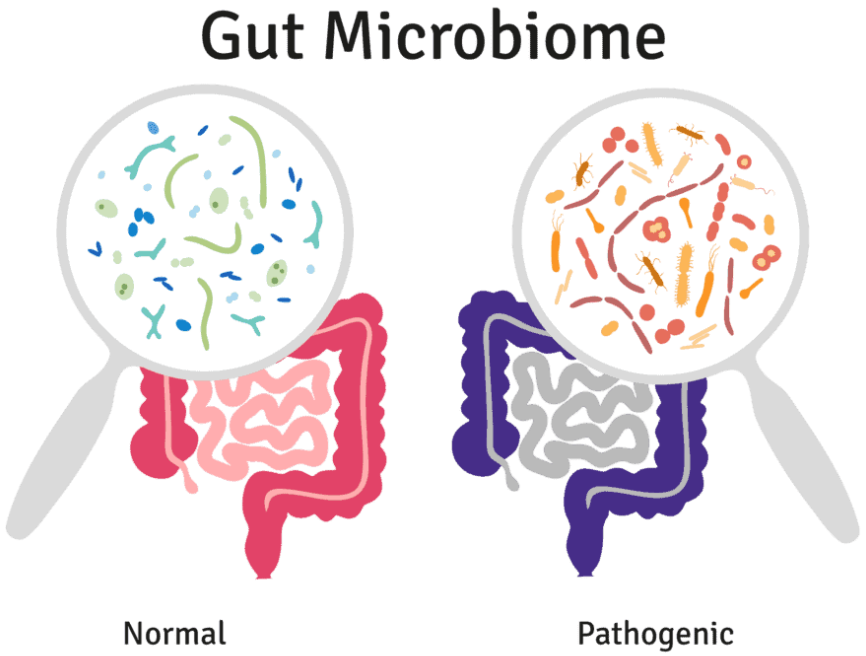
Exercise – Try to be active every day

Dysbiosis

Several studies have shown dysbiosis as a factor in all stages of NAFLD, including fatty liver, NASH, advanced fibrosis and also cirrhosis and hepatocellular carcinoma

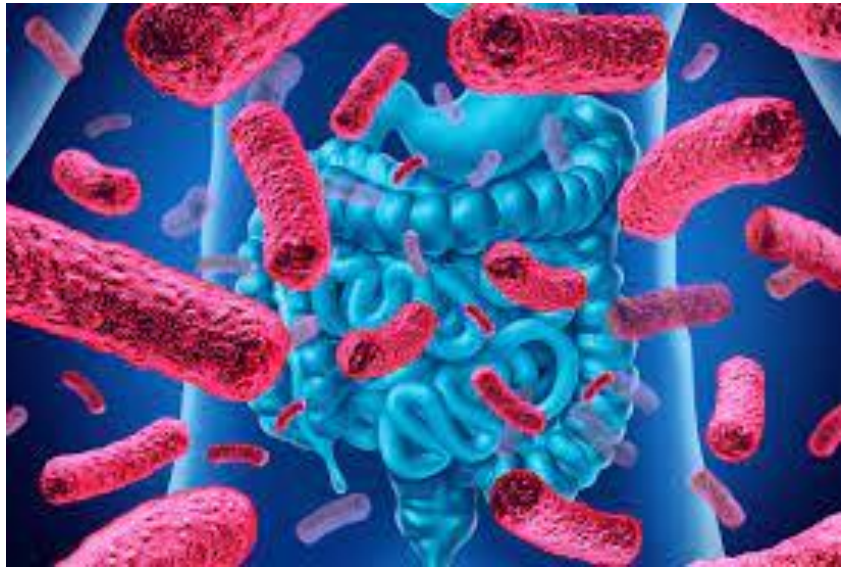
Therefore: It’s considered a biomarker, too

Also NAFLD patients have lower diversity than healthy controls



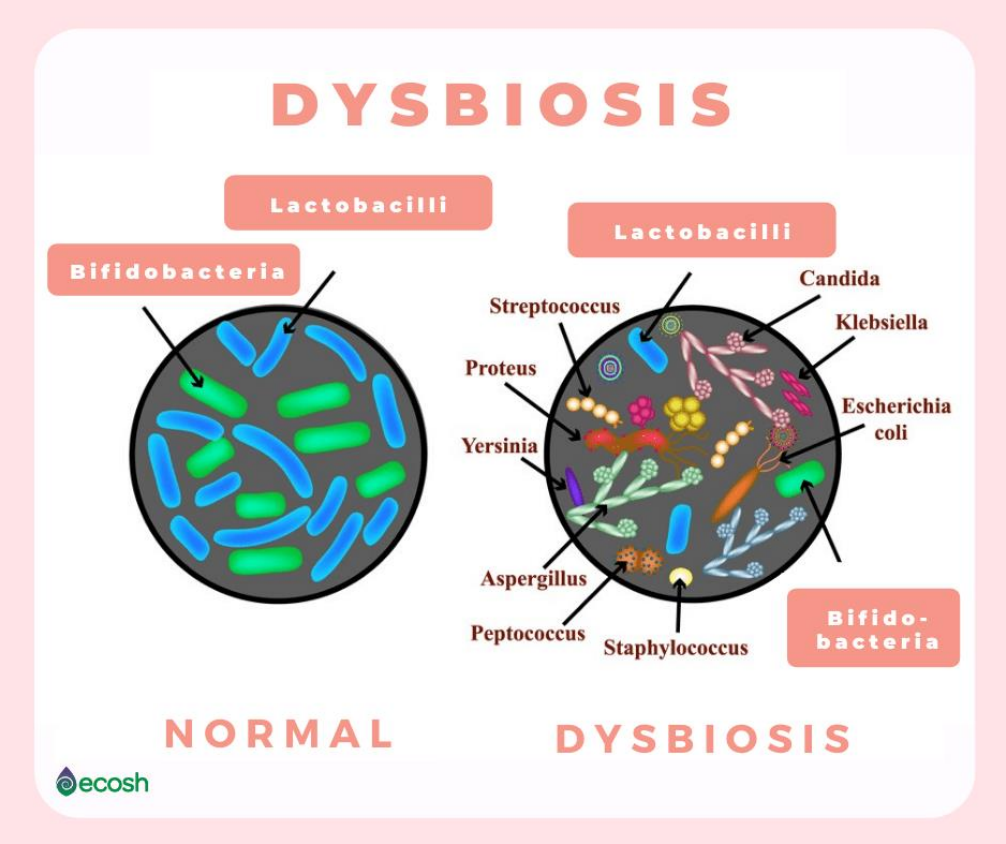
Specific changes in microbial diversity, such as increased Proteobacteria and decreased Firmicutes, are associated with the severity of NAFLD

The gut microbiota influences NAFLD through mechanisms such as energy homeostasis, endocannabinoid system modulation, choline metabolism, bile acid metabolism, endogenous ethanol production, and inflammatory pathways.



Dysbiosis contributes to low-grade inflammation, insulin resistance, and NAFLD progression

Gut microbiota also affects appetite signaling and fasting-induced adipose factor suppression. Understanding these interactions may inform therapies targeting gut microbiota to manage NAFLD



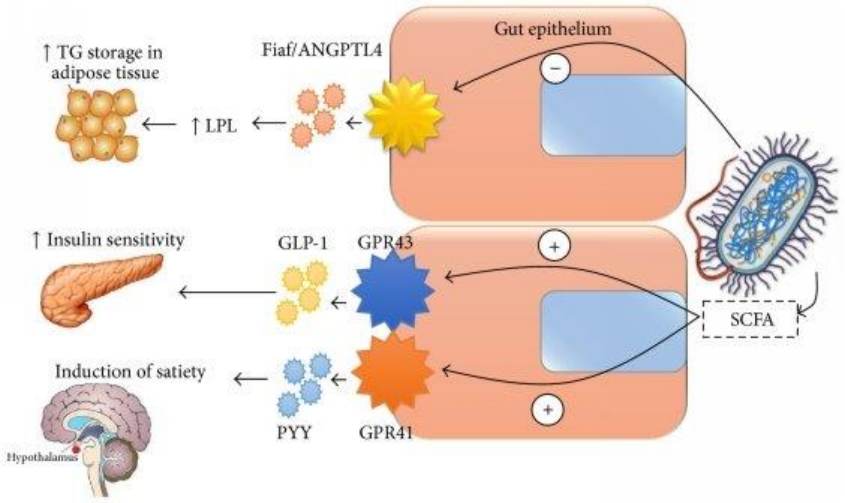
Dysbiosis can promotes an increase in the absorption of monosaccharides in the gastrointestinal tract

This can accelerating *de novo* lipogenesis (DNL) which increase the conversion of carbs to fat in the liver

Gut microbiota can also suppress the fasting-induced adipocyte factor (FIAF) produced by intestinal cells

FIAF is involved with glucose tolerance, insulin sensitivity and fat metabolism

FIAF increases with fasting and decreases with high-fat feeding



Endocannabinoid System

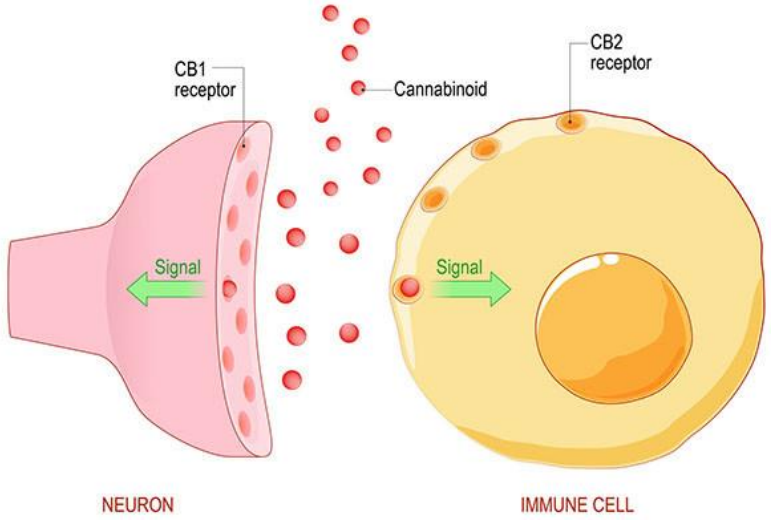
Cannabinoid (CB) receptors which are present in the brain and peripheral tissue including the liver

Have a role in proliferation, differentiation, and secretion of adipocyte hormones - connected to insulin sensitivity and anti-inflammatory effects

Cannabis is protective effects against NAFLD

Overactive CB1 receptors have been linked to increasing food intake & obesity, insulin resistance, fat accumulation

Dysbiosis may contribute to this overactivation by influencing the production of endocannabinoid-like compounds in the gut

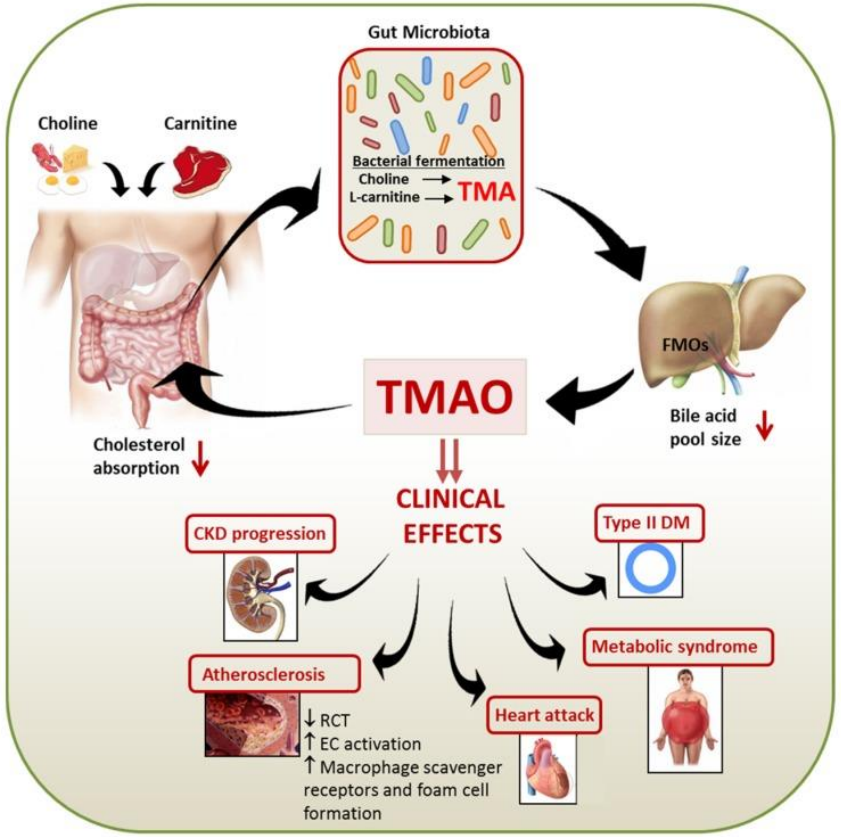


Choline deficiency is known to cause chronic liver disease

Enzymes produced by the gut bacteria — (changed by a high-fat diet)—convert dietary choline into toxic metabolites, namely dimethylamine and trimethylamine

These are converted to TMAO in the liver which increases inflammation and is connected to NAFLD

TMAO has been linked to red meat and heart issues



What can help

Resistant Starch

Studied as a treatment for NAFLD

4-month randomized placebo-controlled clinical trial in individuals with NAFLD

Intrahepatic triglyceride content (IHTG) is a marker for how well triglycerides are removed from the liver

Dysregulation of removal allows for fat accumulation in the liver - correlated with NAFLD

RS lowered IHTG by 5.89 % after accounting for weight loss

Blood branched-chain amino acids (BCAAs) and gut microbial species, in particular *Bacteroides stercoris*, significantly correlated with hepatic steatosis and liver enzymes

These were also reduced by RS

Plus fasting blood glucose was reduced (could be due to weight loss since the control group also saw a reduction)

Fasting and post-prandial insulin levels decreased

LPS, TNF-alpha, and IL1-B all connected to inflammation were also lowered

RS affected other aspects associated with the liver

It did so by altering the microbiome bacteria composition

Probiotics can also be helpful in a protocol

Ingestion of Lactobacillus strains, such as L. acidophilus, L. fermentum and L. plantarum, slows the progression of nonalcoholic steatosis by lowering cholesterol

Commonly found in probiotic formula

Promising results in reducing serum ALT levels and improving fibrosis scores.

Caffeine may reduce liver fibrosis by decreasing lipid accumulation, increasing antioxidant capacity, and suppressing inflammation

Chlorogenic acid, a coffee constituent, shows antioxidant and anti-inflammatory properties. Studies on its effects are conflicting, with some indicating potential worsening of inflammation and steatosis

Coffee: Inverse relationship between coffee consumption and NAFLD progression observed in multiple studies

Increases production of antioxidant proteins, reduces oxidative stress, and has antifibrotic effects

Meta-analysis suggests decreased risk of NAFLD and fibrosis with regular coffee consumption

Green Tea: Main therapeutic agent, epigallocatechin-3-gallate (EGCG), exhibits antioxidative and anti-inflammatory effects

Regulates hepatic lipid homeostasis through various pathways

Clinical studies show improvements in liver enzymes and inflammatory markers

Ginger exhibits antioxidant, anti-inflammatory, and insulin-sensitizing effects, potentially managing NAFLD

Animal studies suggest ginger extract may reduce hepatic steatosis and inflammation, but further clinical trials are needed to confirm these findings and establish optimal dosages

Omega-3 PUFAs EPA and DHA demonstrate anti-inflammatory, antioxidant, and lipid-lowering properties

Clinical trials have shown benefits in improving liver enzymes and hepatic fat content for NAFLD patients

Phosphatidylcholine, a cell membrane component, is considered a potential NAFLD treatment due to its role in lipid metabolism

It may enhance liver function and reduce inflammation

Fenugreek seed extract has antioxidant, anti-inflammatory, and hypoglycemic effects, potentially beneficial for NAFLD

Animal research indicates a reduction in inflammation and oxidative stress, but more clinical trials are required to validate its efficacy

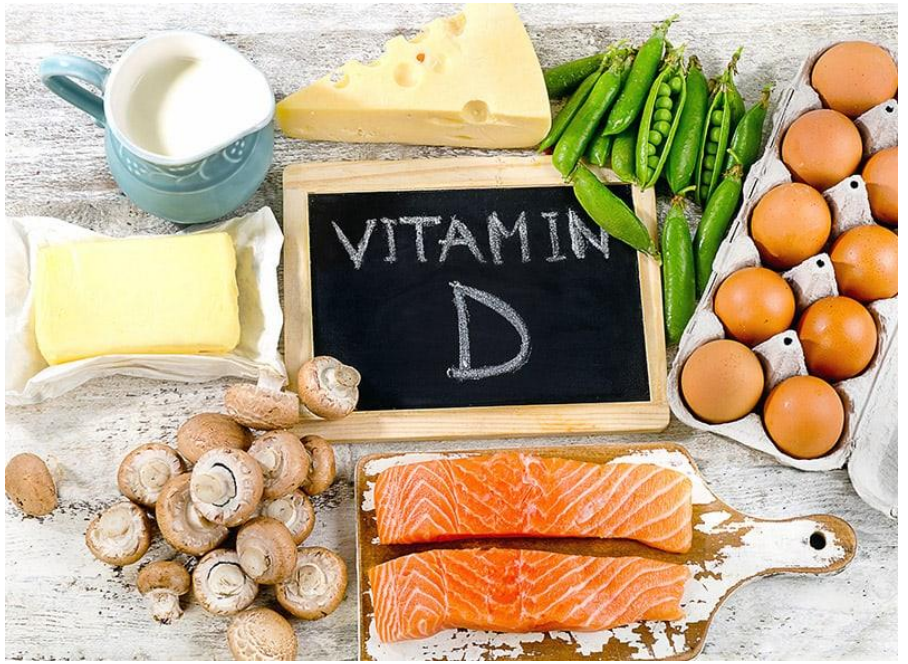
Ascorbic Acid (Vitamin C): is considered for NAFLD treatment due to its potential to counteract oxidative stress

Some animal studies show reductions in hepatic triglyceride accumulation and oxidative stress

Vitamin D deficiency is observed in NAFLD patients, and supplementation is proposed as a potential therapeutic strategy

Preclinical studies suggest protective effects against NAFLD, but further research is needed to confirm clinical benefits and optimal dosages

Alpha-Tocopherol (Vitamin E), due to its antioxidant and anti-inflammatory properties, shows improvements in liver histology, but long-term safety concerns warrant further research, especially in diabetic patients



Silymarin, extracted from milk thistle, has antioxidative and therapeutic effects on NAFLD

Acts as a powerful antioxidant, reduces hepatic de novo lipogenesis, improves insulin resistance, and reduces inflammation

Repairs hepatic cells

Clinical studies suggest positive effects on liver enzymes and fibrosis in NAFLD patients

Reishi mushroom, black cumin seed, and alpha lipoic acid may have similar effects but no studies as much as milk thistle

Resveratrol: Exhibits antioxidative and anti-inflammatory properties similar to milk thistle

Can decrease inflammation, hepatic steatosis, and endoplasmic reticulum stress in NAFLD

Clinical studies show mixed results, with some indicating therapeutic benefits, while others found no improvement

Turmeric (Curcumin): Acts as a powerful antioxidant and anti-inflammatory agent

Improves hepatic steatosis, reduces risk factors, and enhances lipid balance

Clinical trials support its benefits in improving NAFLD parameters

Garlic: Contains active components with antioxidative, anti-inflammatory, and anti-adipogenic effects

Experimental and clinical studies suggest positive effects on NAFLD parameters

Rosemary, Peppermint, Basil, Lavender, Oregano, Sage:

Active components (ursolic acid and carnosic acid) improve lipotoxicity, lipid homeostasis, and exhibit antioxidative effects

Further research needed to determine their effects on NAFLD

Cocoa and cinnamon studied for antioxidative effects, with some positive results in clinical studies.

Ginkgo Biloba regulates fatty acid metabolism, reduces fat accumulation, and decreases oxidative stress

Experimental studies show improvement in NAFLD

Red clover and chamomile may help but the effects on NAFLD are not well understood; more research is necessary

Ginseng: Reduces lipid accumulation, exhibits anti-inflammatory and anti-fibrotic effects

Experimental and clinical studies suggest potential benefits for NAFLD

Lotus, Goji Berry, Astragalus: Experimental studies indicate potential therapeutic use, but no clinical trials yet

Effects on inflammation, lipid homeostasis, and liver function studied

Licorice studied for its potential in lipid homeostasis.

The key to managing this condition:

1. Identify factors that could have led to it
2. Add nutrients that can help improve the situation
3. Do gut work
4. Construct a protocol to add as many of these foods or herbs – one at a time – go slow

The liver is very responsive and the right strategies can make a difference