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Effect of Microbiome Alterations on the Progression & Treatment of Nonalcoholic Fatty Liver Disease

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Topic Introduction

- Nonalcoholic Fatty Liver Disease (NAFLD) is the presence of hepatic steatosis (fat) within the liver which is not caused by alcohol consumption, virus, or medications (Sivell, 2019)

- NAFLD can become · more advanced and lead to liver inflammation which is diagnosed as nonalcoholic steatohepatitis (NASH). NASH was first described in 1980 (Sheka et al., 2020)

- NASH can progress to scarring (cirrhosis) and liver failure, as is seen in patients with long-term alcohol abuse (Mayo Clinic, 2020)

- Risk factors for NAFLD are obesity, dyslipidemia, type 2 diabetes mellitus (T2DM) and metabolic syndrome (Sheka et al., 2020)

- NAFLD is viewed as a multi-factorial disease in which genome-environment interactions, diet, hormonal imbalances, and gut microbiome alterations appear to play a role in the development and progression (Mohammadi et al., 2020)

Topic Importance

- "From 2004 to 2016, there was a 114% and 80% expansion in liver transplant waitlist registration due to NASH for men and women, respectively" (Sheka et al., 2020, p.1175).

- In 2017, lifetime medical costs for U.S. NASH patients were approximately $222 billion (Sheka et al., 2020)

- As rates of metabolic syndrome, obesity, and T2DM rise, it is important for healthcare providers to realize that NAFLD will be more prevalent in patients. Healthcare providers should be knowledgeable about diagnosis and treatment approaches

- Recent research has demonstrated that gut microbiota play a pivotal role in the development of NAFLD and the progression to NASH (Yamada et al., 2017)

Signs & Symptoms

NAFLD symptoms (Mayo Clinic, 2020)
- Fatigue
- Pain/discomfort upper right abdomen
- There are not many signs or symptoms at this early stage, which can make diagnosis difficult

NASH & cirrhosis signs & symptoms (Mayo Clinic, 2020)
- Abdominal swelling (ascites)
- Enlarged blood vessels just under the epidermis
- Enlarged spleen
- Red palms
- Yellowing of eyes and skin (jaundice)

Diagnosis

The following tests can assist in determining disease severity and diagnosis (Mayo Clinic, 2020):
- Complete blood count
- Liver enzyme and liver function tests
- Tests for chronic viral hepatitis
- Celiac disease screening test
- Fasting blood sugar
- Hemoglobin A1C
- Lipid profile, specifically looking at cholesterol and triglycerides
- Abdominal ultrasound (US)
- Computerized tomography (CT) and Magnetic resonance imaging (MRI) (These cannot distinguish between NAFLD or NASH)
- Transient elastography (US that evaluates stiffness/fibrosis of liver)
- Magnetic resonance elastography: MRI with sound waves that creates an image (elastogram) which shows stiffness in body
- Liver biopsy- ***Gold standard**
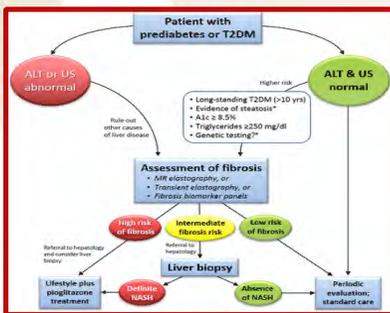
Figure 1: Algorithm for diagnosis of NAFLD and NASH in patients with prediabetes and T2DM in clinical practice (Bril & Cusi, 2017)

Underlying Pathophysiology

Type 2 diabetes (T2DM) and obesity are highly correlated with NAFLD and multiple factors and mechanisms are thought to contribute to disease initiation and progression (Hydes et al., 2020):
- Ectopic fat accumulation
- Insulin resistance in which muscle, fat , and liver cells do not effectively respond to insulin, which leads to poor glycemic control
- Low adiponectin levels, which normally protect against insulin resistance and increase fatty acid oxidation and glucose metabolism
- Increased inflammatory cytokines produced by dysfunctional adipose tissue
- Gut dysbiosis which causes intestinal permeability and activates inflammatory pathways
- Mitochondrial dysfunction
- These different factors cause fat to "accumulate in the liver in the form of triglycerides, leading to an increase in lipotoxicity because of higher levels of free fatty acids and free cholesterol causing mitochondrial dysfunction, oxidative stress, and the production of reactive oxygen species" (Sivell, 2019, p.430).
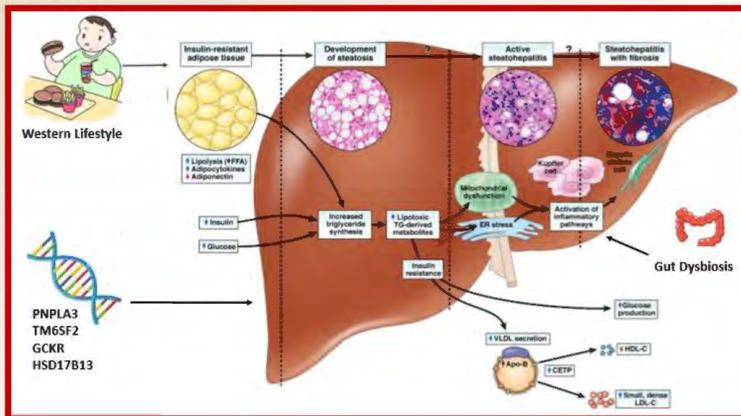

Figure 2: Pathogenesis of NAFLD (Akshintala et al., 2019)

Significance of Pathophysiology

- NAFLD, which can lead to NASH, is "now the leading indication for liver transplant listing in women and is expected to overtake alcoholic liver disease as the leading liver transplant indication for all patients within the next few years" These patients also "have an increased risk of hepatocellular carcinoma" (Sheka et al., 2020, p.1175).
- In the mid 2000's, 20%-30% of the U.S. population met the criteria for NAFLD (Sheka et al., 2020)
- Approximately 3.6 million new cases of NAFLD each year (Sheka et al., 2020)
- NAFLD is a multi-system disease because it relates to increased risks of cardiovascular disease, chronic kidney disease, retinopathy and neuropathy related to diabetes, and extra-hepatic cancers (Hydes et al., 2020)
- Because NAFLD has few signs and symptoms, it is important for healthcare providers to know risk factors and comorbid conditions associated with the development of the disease (see **Figure 3**) and implement appropriate testing and health recommendations

Role of Gut Dysbiosis

- Altered gut flora appears to increase small bowel permeability and causes increased fatty acid absorption and activates inflammatory cytokines, which leads to inflammation and steatosis in the liver (Sivell, 2019)

- It is hypothesized that metabolites produced by certain gut microbiota interact with a host's epithelial lining and immune cells and indirectly affect the process of NAFLD (Liang et al., 2021)

- Lipopolysaccharides (LPS), known as endotoxins, which are found in the cell walls of gram-negative bacteria, are found to be at higher levels, systemically, in NAFLD patients and have been shown to promote liver inflammation (Inamine & Schnabl, 2018)

- "Probiotic treatment with *Lactobacillus* spp. and *Bifidobacterium* spp. improved bacterial dysbiosis and ameliorated liver injury and/or inflammation in both human and animal models" (Inamine & Schnabl, 2018, p.696)

- Using this research, healthcare providers can evaluate the interaction between gut microbial disorders, environmental factors, and diet and assist a patient in developing treatment plans to improve NAFLD progression (Liang et al., 2021)

Figure 3: Comorbidities & Other Factors that Drive or Inhibit NASH progression (Cotter & Rinella, 2020)

Comorbidities	Genetic	Microbiome products	Nutrition and behavior
• **Obesity**	• **PNPLA3**	• ETOH	• Alcohol
• **Metabolic syndrome**	• **TM6SF2**	• Lipopolysaccharide	• Cholesterol
• **Insulin resistance**	• **A1AT Pi*Z**	• Reactive oxygen species	• Fructose
• **Type 2 DM**	• HSD17B13	• Cholesterol oxidation products	• Exercise
• Dyslipidemia	• LYPLAL1	• Butyrate	• Coffee
• **Hypertension**	• GCKR	• Acetate	
• OSA	• MBOAT	• Phenylacetate	
• PCOS	• DNA methylation	• Secondary bile acids	
• **Hypopituitarism**	• Chromatin remodeling	• Choline deficiency	
• Low GH	• Non-coding RNAs		
• Low testosterone			
• Thyroid disease			
• LAL-D			
• Iron overload			
• Psoriasis			
• Osteoporosis			

Black = association with evolving evidence

Red = established association

Green = protective

Bold = drives NASH progression

Treatments

- Weight loss, 7-10% loss of total body weight recommended (Hydes et al., 2020)
- Exercise, average-paced walking 3hrs/week substantially lowered mortality risk (Hydes et al., 2020)
- Pioglitazone, glucose-lowering medication (Hydes et al., 2020)
- Vitamin E, antioxidant that protects against oxidative stress (Hydes et al., 2020)
- Avoid saturated and trans fats
- Avoid sugar (fructose) in diet
- Avoid alcohol
- Synbiotics (probiotics and prebiotics) (Inamine & Schnabl, 2018)
- Bariatric surgery (Sivell, 2019)
- Liver transplant if liver failure

Nursing Implications

- Nurses can greatly improve the health outcomes of patients with obesity, metabolic syndrome, insulin resistance, and type 2 diabetes by implementing appropriate and early testing and imaging to determine if NAFLD or NASH is present.

- Educating patients about lifestyle and diet modifications, probiotic/prebiotic usage, and medications, if appropriate, can improve health outcomes-fatty liver can be a reversible process

- Nurses should assess for psychological issues that could be contributing to poor lifestyle choices and assist in coordinating support if needed (Sivell, 2019)

Conclusions

- NAFLD is known as a silent disease and many patients do not experience symptoms until advanced stages

- NAFLD can be driven by a combination of comorbidities, genetic factors, microbiome alterations, and lifestyle choices

- Advanced practice nurses should be knowledgeable about thorough bloodwork and imaging needed to assist in making correct and early diagnoses

- There are no FDA approved pharmaceuticals for NAFLD, but weight loss, exercise, pioglitazone, and vitamin E have been shown to improve NAFLD patient outcomes (Sheka et al., 2020)

- Alterations of the gut microbiome through use of synbiotics show promise in decreasing fatty acid accumulation in the liver and may be a common therapy for treating NAFLD in the future

References

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