Summer 2015

NASH: Non-Alcoholic Steatohepatitis

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is a chronic liver disease which refers to the presence of hepatic steatosis without significant intake of alcohol. Non-alcoholic fatty liver disease develops in a variety of forms from reversible simple steatosis to non-alcoholic steatohepatitis (NASH), which if left unchecked can progress to liver fibrosis, cirrhosis and even develop into hepatocellular carcinoma (Mells et al., 2014).

NAFLD is thought to be nonthreatening, but with progression over several years could lead to NASH. A strong link between obesity and NASH has been shown. In addition to obesity, insulin resistance (type II diabetes mellitus), and hyperlipidemia all common components of metabolic syndrome, is frequently associated with NAFLD (Nseiri, Mograbi, & Ghali, 2012).

If NAFLD goes undetected and progresses, steatohepatitis a serious inflammation of the liver can occur. Steatosis is a term used to describe any condition that allows fat to deposit within the interstitial spaces of an organ. Steatohepatitis comes in two forms. alcohol-related and non-alcoholic related. The distinction of hepatic steatosis lays in excessive alcohol consumption verses little to no alcohol consumption.

Signs & Symptoms

The symptoms of both types of steatosis are the same, but treatments for each are very different. In NASH treatment consist of focus on other lifestyle changes such as diet, exercise, and weight control.

- Early, asymptomatic
- Late, general malaise and fatigue, unintentional weight loss, loss of appetite, nausea, confusion, poor judgement or trouble concentrating
- Diagnosis made based on abnormal liver enzymes and further testing

Underlying Pathophysiology

Although NASH has become more common, its underlying cause is still not clear. The progression of NAFLD to NASH is multifactorial and includes both environmental and genetic factors. The major feature of NASH is fat in the liver along with damaged hepatocytes from inflammation. Three definitive characteristics have been identified in the process of NASH;

- insulin resistance/ hyperinsulinemia
- resistance release of toxic inflammatory proteins by fat cells (cytokines)
- oxidative stress inside liver cells ("Nonalcoholic Steatohepatitis," 2006).

Purposed pathophysiology from steatosis to steatohepatitis to eventual fibrosis of the liver is based on what is called a "two hits" hypothesis. Vonghia, Michielsen, & Francque (2013), "The initial "two hits" hypothesis described insulin resistance as "first hit" that leads to hepatic steatosis and is followed by a "second hit" driven by oxidative stress, which in turn leads to the development of steatohepatitis and fibrosis"(p. 19868).

Vonghia, Michielsen, & Francque (2013), A key role in the development of insulin resistance is played by altered lipid metabolism that generates lipid intermediates, which in turn are able to activate different kinases, such as the mammalian target of rapamycin (mTOR), the inhibitor of κB-kinase (IKK), the c-Jun N-terminal kinase (JNK) and the novel protein kinase C (nPKC). The activation of these kinases has a negative feedback on proximal insulin signaling, contributing to insulin resistance and to a hyperinsulinemic state that further increases de novo liponeogenesis, hepatic lipid accumulation and disease progression. (p. 19868)

The "second hit" developed in this hypothesis is related to the abundance of oxidative stress found in the liver with NASH. Improper clearance of pro-oxidative species manifest as reactive oxidative stress (ROS). Pro-oxidative stress is known to interfere with nucleic acid, protein, and cell membrane function (Vonghia et al., 2013).

More importantly the role of ROS, Tariq, Green, & Hodson (2014), these species can initiate lipid peroxidation by targeting polyunsaturated fatty acids (FAs), resulting in the formation of highly reactive aldehyde products, such as 4-hydroxy-2-nonenal (4-HNE) and malondialdehyde (MDA). These reactive lipid derivatives have the potential to amplify intracellular damage by mediating the diffusion of ROS/RNS into the extracellular space thus causing tissue damage. (p.181)

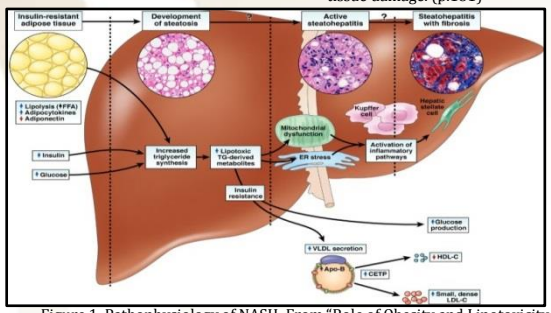
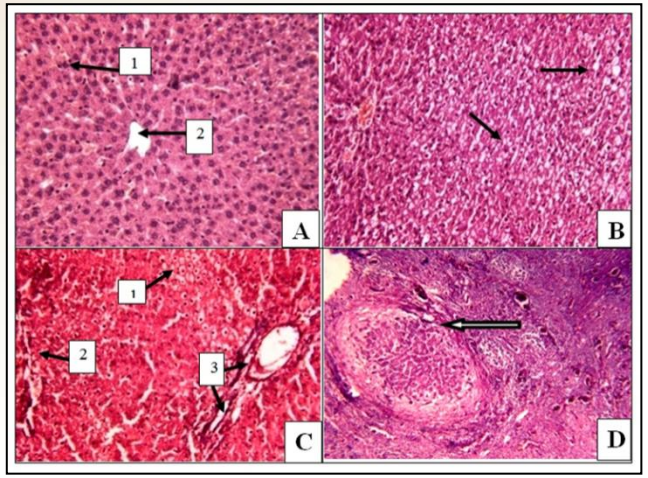


Figure 1. Pathophysiology of NASH. From "Role of Obesity and Lipotoxicity in the Development of Nonalcoholic Steatohepatitis: Pathophysiology and Clinical Implications", by K. Cusi. http://www.gastrojournal.org, Copyright [2012] AGA Institute. Published by Elsevier Inc.

Significance of Pathophysiology

Over the past several years, the incidence of NAFD has been on a steady rise. The rise of detected cases is directly related to the increase incidence of obesity. NAFLD is rapidly becoming the most common liver disease worldwide. Twenty to thirty percent of the general population in Western counties has NAFLD (Gitto, Vitale, Villa, & Andreone, 2015). About 2% to 3% of the general populations have non-alcoholic steatohepatitis (NASH), which may progress to liver cirrhosis and hepatocellular carcinoma (HCC) (Nseiri et al., 2012).

In recent research the role of both innate and adaptive immunity is demonstrating a strong link to the pathogenesis of NASH. For example Kupffer cells (KC), known to contribute to innate immunity are the first responding cells to hepatocyte injuries, leading to tumor necrosis factor-α (TNF-α) production, chemokine induction, and monocyte recruitment all contributing to pro-inflammatory responses of the hepatocytes (Vonghia et al., 2013). As for adaptive immunity, an imbalance in subtypes of T lymphocytes, such as CD4+/CD8+ cells potentiate cytotoxic T cell release further promoting inflammation and destruction of hepatocytes (Vonghia et al., 2013). The above are just two of the many roles both adaptive and innate immunity play in the development of NASH. Continued research and clinical trials provide a promising future of pharmacologic treatments in this disorder.



Normal liver tissue (1) normal hepatocyte and (2) normal central vein in; B) Fat droplet deposition (the arrow ↑) extending in up to 66% indicating steatosis grade 2 C) NASH with (1) fat deposition, (2) portal mononuclear cell deposition indicating inflammation and (3) portal fibrosis in D) loss of normal hepatic architecture with cirrhotic nodule surrounded by fibrous tissue (the arrow ↑)

*Figure 2.*Photomicroscopic pictures of isolated liver tissue. From "Serum Resistin,Vaspin and Chemerin in Rats with Non Alcoholic Fatty Liver Disease: Correlation with Metabolic and Haemostatic Parameters", by K. EL-Kashish, http://article.sapub.org/10.5923.j.medicine.20140304.02.html. Copyright [2014] Scientific & Academic Publishing.

Implications for Nursing Care

Nurse practitioners have the ability to reach the general population, and teach community members preventive methods in decreasing his/her risk for developing NASH. An important part of health care today is screening and surveillance by way of patient education. Nurse practitioners are at the forefront of prevention and promoting healthy lifestyle changes.

There is not one specific test to diagnosis a patient with NASH. A through history and review of associated health risk must be assessed. Patients whom are obese with insulin resistance (type 2 DM), high cholesterol (triglycerides), and metabolic syndrome are at risk for developing NASH. If risk factors are identified additional testing such as blood test including liver function test, abdominal ultrasound, CT scan, and liver biopsy my be indicated for a definitive diagnosis. When further evaluation shows no apparent reason for liver disease (such as medications, viral hepatitis, or excessive use of alcohol) and when x rays or imaging studies of the liver show fat, NASH is suspected.

NASH is almost always a chronic condition and associated with obesity, and type II diabetes. Currently no specific therapies for NASH exist. Prevention and management consist of decrease in alcohol consumption, diet, weight loss and exercise programs. Improved glucose control, along with weight management has shown marked improvements in aminotransferase levels (Perseghin, 2011). In addition to improved liver function, tight glucose control will decrease the effects of hyperlipidemia, and hypertension.

Conclusion

NAFLD affects a considerable number of the general population and is closely associated with metabolic syndrome. Although simple fatty liver disease is seen in about one-third of the population, it is a relatively benign disease, but is associated with an increased mortality rate (House et al., 2013). Of these individuals NASH seems to occur in approximately 3% of the US population but may be found in more than 25% of obese persons (House et al., 2013).

Due to the consequences of the disease a uniform prevention and screening for associated risk factors should be followed. Ongoing research and large clinical control trials are being investigated to provide healthcare providers and patients with more targeted treatment modalities. Finally, studies on the multifaceted pathogenesis of NASH may not only improve our understanding of the mechanisms involved in NASH progression, but also may lead to innovative therapeutic strategies to treat this condition. Prevention is key to reducing the harmful outcomes of NAFLD to NASH.

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