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NASH Syndrome

The Coming Epidemic

ABSTRACT

Nonalcoholic steatohepatitis (NASH) is a serious and rapidly growing problem affecting a population that was not previously recognized as high risk. Although treatments are limited, shedding light on those with a predisposition may allow for primary prevention, as there is presently no cure other than liver transplant. This study examines the risk factors, genetic predisposition, pathophysiology, and treatment options.

Introduction to the Disease

Nonalcoholic fatty liver disease (NAFLD) is fast becoming a disease of first-world countries, where high fat food is rarely a scarcity, and lives continue to become more sedentary. It affects a known 100 million Americans, with many others undiagnosed because they are asymptomatic (Rinella et al., 2014). Nonalcoholic steatohepatitis (NASH) is a deadly subset disease of those diagnosed with NAFLD. It involves cellular restructuring of the liver in the presence of inflammatory processes, which can lead to hepatocellular carcinomas, cirrhosis, and often death. NASH is becoming more prevalent, with more than 25 million known cases in the United States alone (or ~12% of the adult population).

NASH is comparable to alcoholic cirrhosis/hepatitis, as it can follow the same sequelae of complications (portal hypertension [HTN], esophageal varices, increased bleeding times, decreased albumin, causing ascites, fluid shifts, malnutrition), but the risk factors for these diseases are different. According to Rinella et al. (2014), there is no consensus regarding the amount of alcohol ingestion that needs to occur to make this disease alcoholic steatohepatitis versus nonalcoholic steatohepatitis. As more is learned about NASH, as well as the development of less invasive diagnostic tests, new treatments will likely develop. At this point, the gold standard for definitive diagnosis is a liver biopsy, but, unfortunately, it is a high-risk and costly procedure, especially in light of increased bleeding times. Once a diagnosis of NASH is made, treatment continues to be mostly symptom management, and only marginally effective. Many of those affected may need to be evaluated for liver transplant. How this disease progresses is different in each case and is the subject of much discussion. This article discusses an overview of the risk factors, cellular and genetic levels of the process, immune response, complications, and treatment of NASH.

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Risk Factors

Lifestyle choices increase the probability of developing NASH; therefore, there is an opportunity to decrease risks, minimize symptoms, and perhaps prevent the disease entirely. Both NAFLD and its progression into NASH are seen almost simultaneously, with at least some of the components of metabolic syndrome. Metabolic syndrome is a combination of conditions that include insulin resistance/Type II diabetes, HTN, hyperlipidemia, and obesity. In the literature, there is a link that NAFLD is the hepatic component of the metabolic syndrome diagnosis (Takahashi & Fukosato, 2014).

The primary risk factors of NASH include obesity (body mass index [BMI] >30), insulin resistance, Type II diabetes, "central adiposity" (Paskos & Paletas, 2009, para. 12), elevated triglycerides, decreased high-density lipoproteins, and HTN. It is the combination of many of these risk factors, not usually just one, that increase the risk of disease. Unfortunately, many of these risk factors cannot be teased apart. They come together as a symbiotic relationship, such as obesity coupled with insulin resistance, and with these come HTN and hyperlipidemia.

Perhaps, the strongest risk factors for the development of NASH syndrome are obesity and insulin resistance. Insulin resistance, when diagnosed, is almost exclusively found in those who are clinically obese. Those who are insulin resistant have an abundance of adipose tissue in their abdominal area. This group tends to develop the other criteria of metabolic syndrome and run a much greater risk of developing NASH.

Obesity, in itself, is probably the largest risk factor to every possible disease. Although obesity is the most modifiable of all of the risks of NASH, the likelihood of developing the disease with just this risk factor is much less likely than those who have insulin resistance. Many of those diagnosed as clinically obese do not necessarily have the criteria for metabolic syndrome. While the presence of excess lipids is important, where these lipids are stored is even more critical. Even a population that does not meet the criteria of obesity may still have insulin resistance and metabolic syndrome, putting them at a much higher risk of NASH. It is this author's belief that insulin resistance is the most critical risk factor for the development of this disease. Knobler et al. state that insulin resistance is "more closely related to hepatic fat, rather than BMI, suggesting an independent role of insulin resistance" (Cave et al., 2007, p. 188).

It would be easy to correlate the rise in NASH cases with the overall increase in obesity worldwide. However, the diagnosis of NASH has increased at a rate five times greater than that of obesity. This leads to the strong suspicion that NASH is not primarily driven by obesity but must be multifactorial (Hawkey, Bosch, & Richter, 2012).

Role of Genetics and Epigenetics

NASH develops from by a combination of genetic and environmental factors. A large percentage of those diagnosed with this illness have common genetic markers that are related to lipoprotein metabolism. Most often, it is the combination of both genetics and epigenetics that make the "perfect storm" to create the right conditions to alter the landscape of the liver.

Heredity appears to play a significant role in the development of NAFLD, as genetics plays a role where adipose tissue is stored in the body. Fatty liver is much more common in Hispanics and Caucasians than it is in African Americans. Although all three of these groups can develop metabolic syndrome and diabetes, they have significant genetic differences in how their bodies store fat. Genetically, it appears that altered lipoprotein metabolism is related to a lipoprotein gene (Bhattacharya et al., 2013). This genetic component on the metabolism of the lipoprotein leads to a more likely scenario of the development of NAFLD and, more critically, the continued liver destruction of NASH.

The PNPLA3 gene has been strongly linked to the development of steatosis and progressive liver disease. This gene has poorly understood properties as to why it may cause steatosis, but this does help us understand why different ethnicities are more susceptible to developing NASH. This genetic finding is linked to steatosis, independent of BMI, and metabolic syndrome risk factors. The Hispanic population has the highest incidence of PNPLA3 (Koppe, 2014).

Serum cytokeratin-18 (CK-18) and other genetic markers such as fibroblast growth factor 21 (FGF21) are being evaluated for their ability to assist in noninvasive testing of the presence of NASH, separate from NAFLD. At this point, although this information is helpful, it does not adequately separate abdominal inflammation with hepatic inflammatory processes (Dietrich & Hellerbrand, 2014).

However, there must be specific external, environmental factors that progress NAFLD to a diagnosis of NASH. By the exposure to multiple triggers of inflammation, and particularly the inflammation of the liver, there becomes a catalyst for a NASH diagnosis. A genetic predisposition to NASH seems to be linked to the body's fat metabolism and specific alleles that set the body up for inflammatory responses of the liver. This predisposition along with the addition of fatty diet and metabolic syndrome can create the foundations of disease (Trovato, Cantalano, Musumeci, & Trovato, 2014).

Pathophysiology/Immunology

Criteria for Diagnosis

For a definitive diagnosis of NASH to occur, there must be a liver biopsy and examination of cellular pathology. Hepatocytes will exhibit small drops of lipids in their cytoplasm, called steatosis (Takahashi & Fukosato, 2014). There also must be an identification of ballooned hepatocytes, a finding that is indicative of cell death. Lobular inflammation with or without liver fibrosis is the final piece that must be present for the diagnosis of NASH (Rinella et al., 2014).

There are multiple actions that occur on the cellular level, and many of them are not completely understood. The accepted theory up until recently is that of a "two-hit" progression. It had been theorized that an overabundance of triglyceride storage in the hepatocyte cells (NAFLD) may progress to trigger an inflammatory response, causing steatosis. Most recently, it has become evident that this disease is much more complex and involves "multiple hits" such as inflammatory responses and genetic components that likely occur to induce NASH (Takaki, Kawai, & Yamamoto, 2014).

Mitochondrial Changes and Oxidative Stress

The overabundance of lipids in the cells of the liver has a direct and damaging effect on the hepatocyte mitochondria. Because the mitochondria are the primary source of the creation of ATP for the cell, the altered organelle experiences inhibited electron flow. This causes an increased production in the reactive oxygen species, causing even more oxidative stress and damage to the cells (Cave et al., 2007).

Oxidative stress is also related to the tumor necrosis factor (TNF), by causing increased inflammation and regulating insulin resistance. TNF is increased with the onset of mitochondrial dysfunction (Gitto, Vitale, Villa, & Andreone, 2015). These stages appear to be a vicious cycle, as the increase of oxidative stress causes an increase in mitochondrial dysfunction, causing more oxidative stress, more inflammation, and increased lipid storage.

Bacterial Translocation

Microbial changes in the intestine have been found to play a significant role in many chronic, inflammatory diseases and in that of NASH. Diets rich in fat and sugar cause gut bacteria to produce an increased amount of endotoxins. These toxins can change the permeability of the intestinal wall and signal changes to the portal vein and liver, causing an inflammatory response in the hepatocytes. This process is called bacterial translocation (Takaki et al., 2014). Bacterial translocation puts a more tangible cause and effect on how poor dietary choices can directly cause harm to the liver.

Cytokines

Visceral fat correlates strongly with inflammatory response and cytokine release, causing floods of neutrophils to the liver tissues, which is then a catalyst for a progression from NAFLD to NASH. Increased levels of interleukin 17, as well as decreased levels of adinopectin and leptin, are quite frequently observed. Adinopectin and leptin deficiencies have been found to correlate with increased visceral adiposity (Takaki et al., 2014).

Lipotoxicity

Increased levels of free fatty acids (FFAs) are caused by insulin resistance and an abundance of adipose tissue. These FFAs in the liver lead to increased triglyceride synthesis, causing increased lipid metabolites that cause lipotoxicity, increased inflammation, and a further escalation in the cycle of the disease (Koppe, 2014).

Endoplasmic Reticulum

Stress on the endoplasmic reticulum (ER) is caused by increased lipid storage, and a subsequent loss of homeostasis in the cell, affecting the phospholipid in the ER membrane. This causes an unfolding of the ER, which over time leads to cell death. Continued hepatocyte death leads to worsening insulin resistance and worsening NASH (Koppe, 2014).

Accepted Treatments of Disease

Unfortunately, there is no cure for NASH, other than liver transplantation. For severe NASH with cirrhosis, suitable patients may be placed on a transplant list. It is important to ascertain if the patient carries the PNPLA3 genotype, as there is a risk of developing NASH in the transplanted liver. Early studies indicate that the risk of developing the disease in the transplanted liver is higher when the recipient is positive for PNPLA3 genotype rather than the donor organ being positive (Koppe, 2014).

The use of statins, although helpful for patients with dyslipidemia, has unclear benefit in improving NASH. In small studies, they do not seem to effect the overall progression of disease. Pioglitazone, used to decrease circulating blood glucose, may decrease the inflammatory response in the liver but does not improve hepatocellular ballooning or fibrosis. In addition, these pharmacological interventions may do more harm with their overall side effects and interactions (Mouzaki & Allard, 2012). However, these medications may help improve the underlying risk factors of the development of NASH syndrome, and for that reason it is important to evaluate their use on a case-by-case basis. There have been many trials of off-label use of other medications, such as those that promote weight loss by binding with lipids, with no affirmation that they provide anything other than anecdotal improvement (Gitto et al., 2015).

Vitamin E as an antioxidant has provided some modest improvement in disease progression, although doses higher than 400 IU daily show risks of increased mortality. It shows promise in decreasing overall lobular inflammation and steatosis but does not improve fibrosis (Gitto et al., 2015). For these reasons, it may prove to be an effective addition to the treatment of the disease, with less potential for adverse reactions.

Treatment Argument

The first-line therapy that is most accepted is a program founded on diet and exercise modification. Unfortunately, for most patients, it is harder to commit to a treatment plan than it is to take medications. As has been well documented in nearly every chronic disease, the addition of a lower fat, no concentrated sweets, calorie-restricted diet, along with a moderate exercise routine, provides the best treatment, whether as first-line or adjunct therapy.

A 6-month study where subjects were each assigned diet, exercise, or both combined showed that a gradual weight loss over a period of time was achieved in each group, and 50% of those involved showed histological improvement in their disease, whereas 25% showed no discernable symptoms of NASH (Gitto et al., 2015). This provides some powerful evidence that healthy diet and exercise are the single best approach to treating this serious disease.

Unfortunately, practitioners have been prescribing diet and exercise to their patients, with limited success in long-term adherence. Providing solid education, behavior modification programs, and accountability tools may offer assistance. NASH proves to be a terminal disease for many who are diagnosed. Providing patients the knowledge that allows them to empower themselves to make healthy choices to protect their liver, and even reverse the early signs of NASH, gives control back to the patient in a situation that may seem out of their control.

Complications of Disease

The progression of NASH leads to worsening liver function, cirrhosis, ascites, and death. As the liver becomes more steatotic, it worsens insulin resistance, exacerbating diabetes and cardiovascular disease. As insulin resistance increases, it then contributes to increased inflammation and lipid encroachment on an already diseased liver. One third of patients with NASH progress to fibrosis and cirrhosis. There is a 25% 10-year mortality rate, and 5% of patients develop end-stage liver disease or hepatocellular carcinoma (Dietrich & Hellerbrand, 2014).

The complications of NASH are those of a diagnosis of liver insufficiency. Cirrhosis causes portal vein hypertension, which can then lead to ascites. Portal vein hypertension is due, in part, to the atrophy and scar tissue in the liver and increased vascular resistance. This causes production of vasodilators, leading to decreased blood pressure and flow to the kidneys. This stimulates the renal-angiotensin system, allowing increased fluid in the bloodstream to raise blood pressure, all of these lead to a leaking of fluid from the intravascular space and into the abdominal cavity, causing ascites (Fullwood & Purushothaman, 2014).

Summary

NASH is becoming an epidemic of the 21st century, now the most prevalent liver disease. A combination of dietary habits, sedentary lifestyle, inflammation, and genetic components makes this disease multifactorial, providing the opportunity for treatment to occur on many different fronts. Treating the inflammatory response is the single most important factor in controlling or preventing NASH syndrome. Although diet, exercise, and prudent use of medications may be helpful, they must be part of a long-term lifestyle changes to have success. Further research is necessary to improve treatment options, symptom management, and optimize quality of life. ✪

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