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Nonalcoholic fatty liver disease, a potentially fatal obesity-related condition, affects more than 70 million people in the United States. Nurses are well-positioned to impact this genetically influenced disease by increasing awareness, providing patient education, and advocating for affected persons.

Nonalcoholic fatty liver disease (NAFLD) is a rapidly emerging worldwide public health concern strongly associated with obesity, insulin resistance/diabetes type 2, and the metabolic syndrome (Younossi et al., 2011). It is the most common cause of liver disease in the world (World Gastroenterology Organisation [WGO], 2012). Defined as a total liver weight comprised of more than 5% fat, NAFLD can progress from simple fatty liver disease to nonalcoholic steatohepatitis with or without fibrosis, liver cirrhosis, liver cancer, or liver failure resulting in premature death (Levene & Goldin, 2012). The development and progression of NAFLD is influenced by genetic and environmental factors that may have implications for health (Romeo et al., 2008; Romeo et al., 2009; Valenti et al., 2010). A description of NAFLD is provided in this article, with information about the genetic basis of NAFLD and potential implications of genetic health information related to NAFLD. Nurses' critical role in health promotion, disease prevention, and management of chronic disease in persons with NAFLD also will be discussed.

Description of Health Problem

History

Nonalcoholic fatty liver disease first was described in the 1950s following liver biopsy in patients who did not drink alcohol but developed liver cirrhosis with fatty liver changes similar to those of alcoholic fatty liver (Westwater & Fainer, 1958). In 1980, Dr. Ludwig of the Mayo Clinic named this condition of fatty liver changes in obese persons *nonalcoholic steatohepatitis* (NASH); it now is recognized as the inflammatory stage of NAFLD (Ludwig, Viggiano, McGill, & Oh, 1980). In recent years, NAFLD has become more prevalent, coinciding with the obesity epidemic (WGO, 2012).

Natural History

Incidence and Prevalence

The incidence of NAFLD is difficult to estimate as no diagnostic laboratory tests are available to confirm its presence (WGO, 2012). Although persistent elevation of liver enzymes, such as aspartate transaminase and alanine aminotransferase, often is used to trigger evaluation workup for a diagnosis of NAFLD, estimates of the true incidence of this condition are difficult because normal liver enzymes may be present in people with NAFLD (Rafiq & Younossi, 2009; WGO, 2012). Unlike other equally common diseases (e.g., obesity, diabetes), NAFLD is not a diagnosis found in national databases such as the National Health and Examination Survey (NHANES). Nonetheless, NAFLD is considered a global health concern with an estimated worldwide prevalence from 2.8% (diagnosed by aminotransferase elevation) to 46% (diagnosed by imaging or liver biopsy) (Lazo & Clark, 2008).

Nonalcoholic fatty liver disease and obesity have been observed in many developed countries (WGO, 2012). Worldwide prevalence of obesity is estimated at 1.46 billion adults, suggesting over 292 million adults have NAFLD (Vernon, Baranova, & Younossi, 2011). The U.S. prevalence of NAFLD is estimated at 63 million people, compared to 47 million with metabolic syndrome and 25 million with diabetes mellitus as diseases commonly associated with NAFLD (American Heart Association [AHA], 2010; Centers for Disease Control

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TABLE 1.
NAFLD by Race/Ethnicity

Race/Ethnicity	Prevalence	Participants in Study	Study	Study Type
African American	45%	2,349 - to reflect Dallas, TX population; 32.1% Caucasian, 48.3% African American, 17.5% Hispanic	Browning et al., 2004 Victor et al., 2004	Secondary analysis of Dallas Heart Study participants in whom H-MRS was available
Caucasian	33%			
Hispanic	24%			
African American	35.1%	328; majority of patients with NAFLD were male (58.9%), significantly older, and heavier with higher prevalence of HTN and diabetes	Williams et al., 2011	Prospective study
Caucasian	44.4%			
Hispanic	58.3%			
African American	13.5%	12,454; participants of NHANES	Lazo et al., 2013	Ultrasonography from NHANES-NAFLD defined as presence of hepatic steatosis on ultrasonography in the absence of elevated alcohol usage
Caucasian	17.8%			
Hispanic	24.1%			
African American	11.6%	9,675; participants of NHANES	Schneider, Lazo, Selvin, & Clark, 2013	Cross-sectional study of NHANES
Caucasian	12.5%			
Hispanic	21.2%			
African American	23.1%	3,846; participants of NHANES	Smits, Ioannou, Boyko, & Utzschneider, 2013	NAFLD determined by increased liver fat by ultrasonography data derived from cross-sectional study (NHANES)
Caucasian	29.8%			
Hispanic	39.4%			
American Indian and Alaskan Native	31% of patients with chronic liver disease 2% of general population	26,166	Fischer, Bialek, Homan, Livingston, & McMahon, 2009	Retrospective cross-sectional study from electronic medical records of Alaska Native Medical Center

and Prevention, 2013; U.S. Census Bureau, 2013; WGO, 2012). Nonalcoholic fatty liver disease particularly affects persons who are obese; approximately 75%-92% of them have NAFLD (WGO, 2012). Prevalence projections from the NHANES (1988-2008), which used elevated liver enzymes and absence of other liver disease to determine a NAFLD diagnosis, indicate over 50% of U.S. residents will have NAFLD by 2030 (Baranova et al., 2011; Younossi et al., 2011). This underscores the need for research of this rapidly growing disease.

Race/Ethnicity, Sex, and Age

Nonalcoholic fatty liver disease occurs in both sexes with nearly equal frequency, and in children as well as in adults (Sanyal, 2011; Vernon et al., 2011). It is more common in the 4th-6th decades of life, but occurs over time (Vernon et al., 2011). In a recent cohort study of 39,500 adults, increasing age was identified as an independent predictor of NAFLD (Younossi et al., 2011). A prevalence study found 46% of adults (mean age 54.6) had NAFLD on ultrasound (Williams et al., 2011). Likewise, NAFLD prevalence increases in children as they age (Feldstein et al., 2009).

Nonalcoholic fatty liver disease occurs across all racial and ethnic groups. Because some frequencies are higher than others, race/ethnicity may be a predictor of NAFLD (WGO, 2012). See Table 1 for frequency of NAFLD by race/ethnicity.

While American Indian and Alaskan-native populations have a high prevalence of diabetes and obesity as co-morbidities commonly associated with NAFLD, little NAFLD-related research has been conducted in these groups. However, a population study of Alaskan-native and American Indians with chronic liver disease found NAFLD was the second leading cause of chronic liver disease (Fischer, Bialek, Homan, Livingston, & McMahon, 2009). NAFLD was determined to be the cause of chronic liver disease in 31% of the patients (*n*=1,886), but was found in only 2% of the general population (*n*=26,166). Further research is warranted in these populations to assess the prevalence of NAFLD in all stages of the disease.

Average Duration

Although NAFLD is a progressive disorder, the average duration of the disease is unknown. It is believed to develop over time (Baranova et al., 2011). A longitudinal study followed persons across all stages of the NAFLD illness trajectory. Lower sur-

vival rates were observed in people with NAFLD who presented with NASH or cirrhosis at initial diagnosis (Feldstein et al., 2009). This finding is especially concerning for obese children with NAFLD who may die prematurely as a result of disease progression to end-stage liver disease.

Progression

Nonalcoholic fatty liver disease is characterized by four stages of progression. Simple fatty liver disease is the first stage, in which fat is found in the hepatocytes. The second stage is an inflammatory state of the liver (NASH), which may occur with or without fibrosis. Nonalcoholic steatohepatitis may progress to cirrhosis, one of possible end stages of NAFLD in which scarring of liver tissue results in deterioration of liver function (National Institute of Diabetes and Digestive and Kidney Diseases, 2008). Cirrhosis may lead to liver cancer or liver failure. While not all people with NAFLD will progress to end-stage liver failure or liver cancer, approximately 600,000 people will progress to the cirrhosis stage of this disease which can result in premature death (WGO, 2012; Younossi et al., 2011).

Clinical Features

The clinical symptoms of NAFLD are not understood fully. Historically, NAFLD has been considered an asymptomatic disease, although some evidence indicates fullness or discomfort may occur in the right upper quadrant, as well as fatigue (WGO, 2012). Studies in children have reported symptoms of fatigue, sleep disturbances, and sadness resulting in decreased health-related quality of life; this suggests adults may have symptoms that are yet to be attributed to NAFLD (Kistler et al., 2010).

Persons with NAFLD also may have features of the metabolic syndrome, including obesity (especially upper-body obesity), hyperglycemia, low high-density lipoproteins, and hypercholesterolemia (AHA, 2011). In children with NAFLD and metabolic syndrome, signs and symptoms of fatigue, abdominal pain, hepatomegaly, splenomegaly, and acanthosis nigricans may be present (Feldstein et al., 2009). Persons in the later stages of NAFLD such as liver cirrhosis may exhibit jaundice, itching, ascites, peripheral edema, bruising, and esophageal varices (American Liver Foundation, 2011). More research is needed to determine the symptoms of NAFLD; nurses can use such information to implement early weight loss strategies and manage patient symptoms in the later stages of disease (Houghton-Rahrig et al., 2013).

Current Prognostic and Diagnostic Capabilities

Patients often present to their primary care providers with elevated liver enzymes, leading to an evaluation for NAFLD and possible referral to a gastroenterologist (Rafiq & Younossi, 2009). Liver biopsy is the gold standard for staging and grading the disease (WGO, 2012). Because only a small percentage of people receive a liver biopsy due to potential risks of the procedure, early diagnosis and staging of NAFLD are difficult. As a result, NAFLD often is found incidentally through imaging for other conditions such as acute cholecystitis (Rafiq & Younossi, 2009).

While imaging may detect NAFLD, it is inadequate in determining the stage and grade of disease because tests, such as ultrasound, CT scan, or MRI, cannot detect fibrosis (Mehta, Thomas, Bell, Johnston, & Taylor-Robinson, 2008). Other scanning modalities are emerging, such as the Fibroscan (Echosens of Inner Mongolia; Furui Medical Science Co., France), which measures liver stiffness. Liver stiffness is thought to be influenced by the presence of fibrosis in advanced disease (Wong et al., 2008).

Current Treatments

Current treatments target weight loss through diet, exercise, lifestyle modification, and/or bariatric surgery to reverse NAFLD (Mummadi, Kasturi, Chennareddygari, & Sood, 2008; WGO, 2012). Diets devoid of fructose and transfats should be encouraged. People with NAFLD should obtain moderately vigorous exercise 3-4 times a week. Use of statins, such as atorvastatin (Lipitor®) or pravastatin (Pravachol®), is recommended to control hyperlipidemia (WGO, 2012).

Genetics and NAFLD

Mode of Inheritance

Nonalcoholic fatty liver disease is a multifactorial disorder resulting from the combined effects of genetics and environment. Several lines of evidence point to a genetic contribution to NAFLD. First, NAFLD is highly heritable (h^2=0.850; standard error, 0.325, p<0.0001). In a study of obese children with liver biopsy-confirmed NAFLD, 59% (n=17 of 29) of their siblings had NAFLD compared to 17% (n=2 of 12) of siblings of obese children without NAFLD. Of obese children with liver biopsy-confirmed NAFLD, 78% (n=43 of 55) of their parents also had NAFLD compared to 37% (n=7 of 19) of parents of obese children without NAFLD (Schwimmer et al., 2009). Strong heritability of CT scan-confirmed NAFLD was found in three large family-based cohorts: Amish (0.27, SE 0.08; N=880), Family Heart (0.27, SE 0.04; N=2767), and Framingham Heart Studies (0.26, SE 0.04, N=3070) (Speliotes et al., 2011). Further, the studies by Schwimmer and colleagues (2009) and Speliotes and co-authors (2011) noted familial aggregation consistent with a complex genetic disorder. In addition, a case report from Cleveland Clinic identified an extended family with confirmed NAFLD spanning three generations and suspected NAFLD occurring in over five generations (Carter-Kent & Feldstein, 2010). High heritability and familial aggregation suggest NAFLD has a genetic component.

Susceptibility Genes

Given evidence for heritability, research has attempted to identify specific genes that contribute to increased risk or susceptibility to disease. A Patatin-like phospholipase domain-containing 3 gene (*PNPLA3)*

has been identified as a risk gene for NAFLD (Romeo et al., 2008). The association between NAFLD and the *PNPLA3* (rs738409) polymorphism was discovered using the Dallas Heart Study data, a genetic association study (n=2,111) measuring 9,222 nonsynonymous DNA variants (Romeo et al., 2008; Victor et al., 2004). Romeo and others (2008) identified a polymorphism in the *PNPLA3* (rs738409) gene that is associated strongly with fat content in the liver (p=5.9 x 10^{-19}). In addition, this polymorphism was associated with fat content in the liver after adjusting for body mass index, diabetes, alcohol use, and ancestry (p=7.0 x 10^{-1}).

The nonsynonymous polymorphism (rs738409) in the *PNPLA3* gene is a single base pair substitution of guanine for cytosine, resulting in an amino acid change from isoleucine to methionine at codon 148 position (Romeo et al., 2008). Located on chromosome 22 (22q 13.31), *PNPLA3* (rs738409) encodes triacylglycerol lipase, a protein that is "expressed highest in hepatocytes, followed by skin and adipocytes" (National Center for Biotechnology Information, 2013; Online Mendelian Inheritance in Man, 2011, para. 2). Triacylglycerol lipase mediates triacylglycerol hydrolysis in adipocytes, a process involved in the balance of energy usage/storage in the adipocytes and thought to be regulated by nutrition (Huang et al., 2010). This polymorphism is hypothesized to inhibit triglyceride hydrolysis, resulting in deposits of fat in the liver (He et al., 2010; Romeo, Huang-Doran, Baroni, & Kotronen, 2010).

Several studies support the findings of the Romeo (2008) study (Davis et al., 2010; Kantartzis et al., 2009; Kotronen et al., 2009; Rotman, Koh, Zmuda, Kleiner, & Liang, 2010; Sookoian et al., 2009; Valenti et al., 2010). For example, several implications of the risk (G) allele of the *PNPLA3* (rs738409) gene have been reported. The risk (G) allele of the *PNPLA3* (rs738409) gene was associated with earlier presentation of NAFLD in children (Rotman et al., 2010). In adults, NAFLD severity (e.g., cirrhosis with hepatocellular carcinoma) increased with the presence of two copies of the risk (G) alleles of the *PNPLA3* (rs738409) gene (odds ratio 1.76, 95% CI 1.06-2.92, p<0.05), and is considered an independent predictor of hepatocellular carcinoma occurrence, especially in men (Falleti et al., 2011; Sookoian et al., 2009; Valenti et al., 2010). The frequency of the risk (G) allele of the *PNPLA3* (rs738409) gene also was associated with alcoholic fatty liver disease and increasing severity of liver disease, suggesting the *PNPLA3* (rs738409)-G allele is associated with liver injury (Tian, Stokowski, Kershenobich, Ballinger, & Hinds, 2010). Romeo and colleagues (2008) also discovered a variant of the *PNPLA3* gene (rsrs6006460)-T was associated with lower hepatic fat. This variant was more common in African Americans that in European Americans or Hispanics, suggesting the *PNPLA3* gene (rsrs6006460)-T polymorphism may act as a protective polymorphism that prevents excess fat storage in the liver. Interestingly, Browning and colleagues (2004) were the first researchers to note lower presence of NAFLD in African Americans than in European Americans and Hispanics.

In addition to the frequency of the *PNPLA3* (rs738409)-G allele, other genes or loci correlate with the disease-associated risk of NAFLD. A smaller study of 95 Asian-Indian males found a significant association with the APO3 gene variant alleles (Petersen et al., 2010). Of males who were carriers of the AP03 gene variants C-482T, T-455C, or both, 38% (n=36 of 95) had NAFLD; those with the wild-type variant, that is the variant that occurs most often in the general population, did not (p<0.001). Together, these data suggest NAFLD is a multifactorial disease with potentially numerous genetic influences, most notably, the *PNPLA3* (rs738409) polymorphism (Romeo et al., 2008). Further genetic and environmental research is needed to aid in early identification of patients with NAFLD and those at risk for NAFLD progression for early referral; findings could contribute to tailored interventions.

Implications of Genetic Information for NAFLD

Individual Health Implications

As noted earlier, the risk (G) allele of the *PNPLA3* (rs738409) gene is associated with severity of disease in both children and adults, hepatocellular carcinoma in adults, and an earlier presentation of the disease in children (Falleti et al., 2011; Rotman et al., 2010; Sookoian et al., 2009; Valenti et al., 2010). The use of genotyping for the *PNPLA3* (rs738409-G) allele may provide a means to identify persons at risk for NAFLD progression to NASH or liver cirrhosis/liver cancer (Romeo et al., 2010). Early identification of persons at risk for NAFLD progression would allow earlier intervention.

Hispanics have a genetic predisposition to NAFLD that may explain the higher percentage of Hispanics with NAFLD in the secondary analyses of the Dallas Heart Study (Browning et al., 2004; Romeo et al., 2008; Tian et al., 2010). Davis and others (2010) found an environmental link with a genetically predisposed population. Hispanic children with two copies of the *PNPLA3* (rs738409-G) risk allele are more likely to have more hepatic fat accumulation when dietary sugar intake is high than those with one or no copies of the risk (G) allele. Although this study had a cross-sectional design, findings suggest treatment based on genotype, such as reduced sugar intake for persons with two copies of the "at risk" (G) allele, may be beneficial.

Further research is needed to determine how genotyping of persons with NAFLD may guide effective treatment for NAFLD. Treatment recommendations based solely on genotype currently are premature. However, future research may suggest specific dietary or medication recommendations on this basis.

Public Health Implications

The use of the *PNPLA3* gene variant can provide a means to study the molecular components of NAFLD such as the causes of disease progres-

sion. Romeo and others (2010) suggested the *PNPLA3* gene can be used to discern the interaction between related metabolic conditions, such as insulin resistance and dyslipidemia, vs. NAFLD. Speliotes and colleagues (2011) laid the foundation for future functional studies of polymorphisms related to NAFLD and other associated metabolic conditions.

Kollerits and co-authors (2010) found a correlation between the *PNPLA3* (rs738409) gene variant and elevation in liver enzymes. Future clinical uses of the correlation between elevated ALT and the *PNPLA3* (rs738409) gene may provide a means to measure interventions. These researchers also noted a potential pharmaceutical target for drug trials in the treatment of NAFLD.

Genotyping may be done for children and adults who may be at risk for NAFLD and NAFLD progression, such as persons with obesity or a family history of NAFLD progression, and those with Hispanic ancestry (Tian et al., 2010). Family interventions could be employed early to teach healthy eating habits, and the importance of exercise and frequent follow up, especially in those with one or two copies of the risk (G) allele.

Nursing Implications

Nurses are well-positioned to employ interventions that will impact NAFLD in hospital and community settings. Awareness of NAFLD through patient education is essential to help patients and their families understand the prevalence and severity of this obesity-related disease. Advanced practice nurses (APNs) can provide screening and counseling of patients with NAFLD or genetic predisposition to NAFLD. School nurses may develop health promotion programs with increased physical activity and healthy eating to prevent obesity-related NAFLD and decrease NAFLD in children with existing disease. Physical activity studies of school-aged boys and girls developed by Robbins, Talley, Wu, and Wilbur (2010) may be helpful in developing programs to prevent and treat obesity-related NAFLD in children. Doctorally prepared nurses can assess and implement system changes to facilitate such an activity program (American Association of Colleges of Nursing, 2006). In addition, nurses can teach and role-model obesity sensitivity in all settings.

Medical-surgical nurses also can help patients identify symptoms that signal disease progression in the later stages of disease through patient assessment, follow up, and patient education (Borneman et al., 2010). Nurses can assist patients and families in obtaining timely interventions through self-monitoring through the use of a symptom management toolkit (Given, Given, & Espinosa, 2007). Such interventions may increase the amount of time between discharge and re-admission for older adults through symptom monitoring, as seen in the classic randomized control trial by Naylor and colleagues (1999). Advanced practice nurses can provide case management services to patients with advanced disease to navigate the health care system. They can work closely with medical-surgical nurses to monitor medications for patients with impaired liver function and common comorbid conditions (Nguyen, Cutie, & Pham, 2010).

Conclusion

Nonalcoholic fatty liver disease is a worldwide health concern that may result in premature death if allowed to progress. Identification of the *PNPLA3* (rs738409-G) gene variant offers opportunities for improved risk prediction in persons who may develop NAFLD. Nurses can facilitate health promotion, disease prevention, and chronic disease management for persons with NAFLD. Further research is needed to understand the mechanism underlying the *PNPLA3* genetic association as well as the genetic basis of symptoms in order to develop improved risk prediction models and subsequent tailored interventions (Houghton-Rahrig et al., 2013). MSN

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