Association of Sleep Disorders with Nonalcoholic Fatty Liver Disease (NAFLD): A Population-based Study

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Background: Nonalcoholic fatty liver disease (NAFLD) is a major cause of chronic liver disease. In smaller studies, sleep apnea has been previously associated with NAFLD. The aim of this study was to assess the prevalence and independent associations of sleep disorders in patients with NAFLD using recent population-based data. *Methods:* Three cycles of the National Health and Nutrition Examination Survey (NHANES) conducted between 2005 and 2010 were used. The diagnosis of NAFLD was established as elevated liver enzymes in the absence of all other causes of chronic liver disease. Sleep disorders were diagnosed using sleep disorder questionnaires completed by NHANES participants, and included self-reported history of sleep apnea, insomnia, and restless leg syndrome. The prevalence of sleep disorders was compared between those with and without NAFLD. *Results:* A total of 10,541 adult NHANES participants with complete demographic, clinical, and laboratory data were included. Of those, 15.0% had NAFLD and 7.2% reported having sleep disorders. Of those with sleep disorders, 64.7% reported history of sleep apnea, 16.0% had history of insomnia, and 4.0% had restless leg syndrome. Individuals with NAFLD were more likely to be male (53.8% vs. 45.7%, $P < 0.0001$), obese (50.1% vs. 33.4%, $P < 0.0001$) and had higher prevalence of sleep disorders (9.1% vs. 6.9%, $P = 0.0118$). In multivariate analysis, having any sleep disorder, sleep apnea and insomnia were all independently associated with NAFLD [OR (95% CI) = 1.40 (1.11–1.76), OR = 1.39 (0.98–1.97), and OR = 2.17 (1.19–3.95); respectively)]. *Conclusions:* This large population-based data suggests that NAFLD is associated with sleep disorders. Although the exact mechanism is unknown, this association is most likely through metabolic conditions associated with NAFLD.   (J Clin Exp Hepatol 2013;3:181–185)

Nonalcoholic fatty liver disease (NAFLD) is rapidly becoming the most common cause of chronic liver disease in the Western world.[1] NAFLD is defined by accumulation of liver fat greater than 5% of liver weight in the presence of less than 10 g of daily alcohol consumption. Specifically, NAFLD comprises a broad range of liver injury varying from simple steatosis to nonalcoholic steatohepatitis (NASH), advanced fibrosis and cirrhosis.[2–4] Hepatic steatosis can progress to nonalcoholic steatohepatitis (NASH) and ultimately liver cirrhosis and its complications.[4] Obesity, type 2 diabetes mellitus (DM) and insulin resistance are risk factors often linked with NAFLD.[1–4]

Sleep problems can be caused by a number of conditions including insomnia, restless leg syndrome and sleep apnea.[5–8] Insomnia is a condition generally defined by a positive response to the question "Do you have difficulty falling or staying asleep?"[6] and restless leg syndrome is a condition characterized by an irresistible urge to move one's leg to stop uncomfortable or agitating sensations.[7] Finally, sleep apnea is a condition characterized by abnormal suspensions in breathing or abnormally low level of breathing while sleeping. It has been associated with obesity, glucose intolerance and insulin resistance.[8] In a review study, Alwis et al have linked sleep apnea to increased progression of NAFLD. Specifically, patients with sleep apnea have increased liver enzymes levels as well as worsening histological features independent of body weight.[9] Sleep apnea can be divided into three types: central, obstructive and mixed; however, it is obstructive sleep apnea (OSA) that can not only cause insulin resistance but worsen NAFLD through nocturnal hypoxemia.[10]

The aim of this study is to assess the prevalence and independent associations of sleep disorders in patients with NAFLD using recent population-based data.

METHODS

Study Population

The data used for the study included three continuous cycles of National Health and Nutrition Examination

Surveys (NHANES) conducted between 2005 and 2010. The NHANES data collection is maintained by the U.S. National Center for Health Statistics (NCHS) with the Centers for Disease Control and Prevention (CDC). It includes information about health and nutritional status of the non-institutionalized U.S. population collected via household interviews, physical examination, and laboratory tests, and is currently published in biannual cycles. For our study, public use data files were downloaded from the NHANES website (http://www.cdc.gov/nchs/nhanes.htm). The study was granted an exemption from complete review by the Inova Institutional Review Board.

The inclusion criteria used for the study included the age of 18 years or older, availability of relevant demographic, clinical and examination data, and completed Sleep Disorders Questionnaire. Body mass index (BMI) was measured for all eligible NHANES participants at the time of examination. Furthermore, for the purpose of the study, excessive alcohol consumption was defined as greater than 20 g per day for men and greater than 10 g per day for women during the year prior participating in NHANES and was calculated using the Alcohol Use Questionnaire with self-reported frequency and amount of drinking alcohol.

Diagnosis of Nonalcoholic Fatty Liver Disease

For purposes of this study, elevated serum aminotransferases were defined as ALT >40 U/L or AST >37 U/L in men and ALT or AST >31 U/L in women. Furthermore, possible causes of chronic liver disease (CLD) included chronic hepatitis B (CH–B, defined as positive serum HBsAg), chronic hepatitis C (CH–C, defined as positive anti-HCV) and alcoholic liver disease (ALD, defined as alcohol consumption of 10 g/day or more in women and 20 g/day or more in men during at least a year in the presence of elevated aminotransferases). Using these criteria, presumptive diagnosis of NAFLD was defined as elevated aminotransferases in the absence of any of the causes of CLD listed above. Finally, controls were NHANES participants with normal liver enzymes and no serologic or clinical evidence of CLD as described above.

Sleep Disorders

The diagnosis of sleep disorder was collected from the Sleep Disorders Questionnaire completed by the NHANES participants aged 16 years or older. The NHANES representatives administered this questionnaire during home interview using a computer-assisted personal interview system. In this questionnaire, participants were asked about their sleeping habits, sleep disorders diagnosed by a healthcare provider, and resulting general productivity. For the purpose of the study, we considered those answered positively to the question SLQ060 ("Have you ever been told by a doctor or other health professional that you have a sleep disorder?") as a target cohort of patients with sleep disorders. In the study cycles of 2005–2008, these patients were further asked whether their sleep disorder was sleep apnea, insomnia, or restless leg syndrome. A patient might have reported more than one sleep disorder.

Statistical Analysis

Sampling weights calculated for all NHANES participants were used to account for non-response and unequal selection probabilities for different subpopulation to make the sample representative of the U.S. population. Additionally, stratum and sampling units accounted for the survey design effects using Taylor series linearization. When merging different NHANES study cycles, appropriate selection of sampling weights and adjustment coefficients were applied according to the NHANES Analytic and Reporting Guidelines.[11]

For the purpose of the study, continuous variables such as age measured in years were compared using a *t*-test for a contrasted mean. The prevalence of various parameters, including demographic parameters and different sleep disorders, was compared between subjects with NAFLD and controls by the stratum-specific chi-square test for independence. *P*-values of 0.05 or less were considered potentially statistically significant. Finally, logistic regression was used to identify independent predictors of sleep disorders after adjustment for demographic disparity of the respective target cohorts and controls. All analyses were run with SAS 9.1 and SUDAAN 10.0 (SAS Institute Inc., Cary, NC).

RESULTS

Of the initial study population of 31,034 participants from NHANES 2005–2010, 10,541 were considered eligible for the study. Of those, 1572 individuals (15.0 ± 0.5%) had NAFLD and 8969 were used as controls. The most relevant clinico-demographic differences between individuals with NAFLD and controls are noted in Table 1. As expected, individuals with NAFLD were predominantly male, Hispanic, and 50% more likely obese compared to non-NAFLD controls.

Of the study cohort, 751 individuals (7.19 ± 0.34%) reported having sleep disorders. Of those who reported a type of sleep disorder, 64.70 ± 3.00% had sleep apnea, 15.95 ± 1.97% had insomnia, and 4.03 ± 0.99% reported having restless legs syndrome (an NHANES participant could have reported having more than one sleep disorder). Individuals who reported having sleep disorders were older, predominantly male, Caucasian, and obese (Table 2).

Sleep Disorders and Nonalcoholic Fatty Liver Disease

The prevalence of sleep disorders among individuals with NAFLD was significantly higher as compared to non-NAFLD controls: 9.10 ± 0.87% vs. 6.86 ± 0.35, *P* = 0.0118. On the other hand, no specific sleep disorder

Table 1 Comparison of individuals with and without NAFLD.

	NAFLD	Controls	P
N	1572	8969	
Proportion, %	14.97 ± 0.51	85.03 ± 0.51	
Age, yrs	45.39 ± 0.54	45.92 ± 0.42	0.3114
Male, %	53.76 ± 1.46	45.74 ± 0.58	<0.0001
Caucasian, %	66.84 ± 2.85	70.34 ± 2.40	0.0485
African–American, %	8.51 ± 1.21	11.24 ± 1.36	0.0013
Hispanic, %	18.74 ± 2.21	12.31 ± 1.45	<0.0001
Obesity, %	50.14 ± 1.74	33.42 ± 0.96	<0.0001
Any sleep disorder, %	9.10 ± 0.87	6.86 ± 0.35	0.0118
Sleep apnea, %	3.87 ± 0.71	3.02 ± 0.38	0.1670
Insomnia, %	1.32 ± 0.33	0.68 ± 0.11	0.0591
Restless legs syndrome, %	0.21 ± 0.10	0.19 ± 0.06	0.9119

was particularly responsible for this difference. However, a borderline difference was also observed for insomnia: 1.32 ± 0.33% vs. 0.68 ± 0.11%, $P = 0.0591$.

Of individuals with sleep disorders, the prevalence of NAFLD was 18.94 ± 1.56% compared to 14.66 ± 0.54% in controls without sleep disorders ($P = 0.0118$). The highest prevalence of NAFLD was observed for individuals who reported history of insomnia: 25.57 ± 5.52%.

In multivariate analysis (Table 3), after adjustment for age, gender and ethnicity, NAFLD was found to be independently associated with having sleep disorders [odds ratio (95% confidence interval) = 1.40 (1.11–1.76)] and insomnia in particular [OR (95% CI) = 2.17 (1.19–3.95)]. A close to significant association was also observed for sleep apnea [OR = 1.39 (0.98–1.97), $P = 0.0646$].

DISCUSSION

The study cohort included adult participants from NHANES with complete demographic, clinical, and laboratory data. In this cohort the prevalence of NAFLD[1] and sleep disorders[12] are consistent with what has been previously reported for U.S. general population. In our study, the most common sleep disorder was sleep apnea followed by insomnia and restless leg syndrome. Again, this is consistent with what is reported in the literature.[12] Our data suggest that individuals with NAFLD have higher prevalence of sleep disorders. In our multivariate analysis, having any sleep disorder, sleep apnea and insomnia were all independently associated with having NAFLD.

Our findings suggest that individuals with NAFLD are at increased risk for sleep disorders. This association seems to be independent of components of metabolic syndrome, including obesity and type 2 DM, both associated with sleep apnea as well as NAFLD.[13] The mechanism of liver injury in patients with sleep disorders remains unclear, but Aron-Wisnewsky et al have suggested chronic intermittent hypoxia (CIH) is strongly associated with liver inflammation and liver damage.[14] In addition, Vgontzas et al include the production of inflammatory cytokines leading to oxidative stress in patients with chronic sleep apnea may be a possible mechanism contributing to the pathogenesis of NAFLD. This process may not only contribute to the increased insulin resistance seen in patients with NAFLD but also it may accelerate the process of liver fibrosis leading to the progression to steatohepatitis, cirrhosis and its complications.[15]

In regards to clinical practice, this study provides important insights in evaluating both patients with NAFLD and sleep disorders. First, when assessing the overall cardiovascular and metabolic risk profile of a NAFLD patient, signs and symptoms of sleep disorders should be illicited. If the impression of a positive diagnosis is likely, then the patient should be referred to a sleep center for polysomnography. Second, when assessing the risk profile of a patient diagnosed with sleep disorder, the clinician may consider evaluating the patient for NAFLD. Although treating the sleep disorder may or may not prove beneficial for the patient's liver disease, there is evidence to show that it will improve the patient's cardiovascular and metabolic risk profile.[16]

Table 2 Comparison of individuals with and without sleep disorders.

	Any sleep disorder	Sleep apnea	Insomnia	Restless legs syndrome	No sleep disorders
N	751	291	96	22	9790
Proportion, %	7.19 ± 0.34	4.82 ± 0.41	1.23 ± 0.15	0.31 ± 0.08	92.81 ± 0.34
Age, years	50.95 ± 0.62*	53.86 ± 0.91*	42.61 ± 1.50	52.75 ± 3.65	45.44 ± 0.40
Male, %	52.55 ± 2.22*	63.87 ± 3.25*	23.44 ± 5.71*	29.40 ± 10.72	46.51 ± 0.55
Caucasian, %	74.83 ± 2.72*	80.33 ± 3.18*	53.80 ± 6.51*	86.93 ± 6.20*	69.43 ± 2.43
African–American, %	10.84 ± 1.60	8.29 ± 1.58	13.47 ± 3.75	7.80 ± 4.77	10.83 ± 1.32
Obesity, %	62.18 ± 2.22*	69.66 ± 3.47*	45.01 ± 6.49	58.40 ± 11.26	33.90 ± 0.96
NAFLD, %	18.94 ± 1.56*	18.42 ± 2.38	25.57 ± 5.52*	15.80 ± 7.54	14.66 ± 0.54

*$P < 0.05$ when compared to controls without sleep disorders.

Table 3 Independent predictors of sleep disorders (OR (95% CI)).

	Any sleep disorder	Sleep apnea	Insomnia	Restless legs syndrome
Age, per year	1.02 (1.02–1.03)	1.03 (1.03–1.04)	0.99 (0.97–1.00)	1.02 (0.99–1.05)
Male gender	1.31 (1.09–1.56)	2.27 (1.73–2.97)	0.32 (0.17–0.60)	0.50 (0.18–1.42)
Caucasian	1.30 (1.00–1.69)	1.57 (0.95–2.58)	0.46 (0.25–0.84)	3.67 (0.87–15.46)
African-American	1.36 (1.04–1.79)	1.25 (0.73–2.13)	0.74 (0.35–1.53)	2.36 (0.46–11.98)
NAFLD	1.40 (1.11–1.76)	1.39 (0.98–1.97)	2.17 (1.19–3.95)	1.16 (0.38–3.52)

The limitation of this study is that it is essentially descriptive with little emphasis on mechanistic insight. Future research could combine population-based data with an analysis of the pathogenesis of disease to not only establish an association but also to understand why the association exists. Furthermore, although after exclusion of viral hepatitis and alcoholic liver disease NAFLD is the most likely underlying cause of elevated transaminases. Nevertheless, without imaging or histology, the diagnosis of NAFLD in this study remains presumptive. At the same time, this diagnosis of NAFLD does not include numerous subjects with NAFLD who may have normal liver enzymes. In addition, if the CIH resulting from obstructive sleep apnea is further defined as one of the main subtype of sleep disorder to enhance liver injury, additional studies are needed to define the underlying mechanism.[17] In fact, contributing factors could include hypoxemia and associated oxidative stress, as well as structural deformities of the chest (scoliosis and kyphosis) and any other condition that leads to inadequate ventilation and subsequent periodic hypoxemia. For the clinician, this study provides evidence to the practice of evaluating patients presenting with sleep disorders for chronic liver disease.

In conclusion, our study shows that NAFLD is independently associated with sleep disorders and its subtypes. This important association should prompt clinicians to look for presence of NAFLD in patients with recent diagnosis of sleep disorder. Conversely, patients with diagnosis of NAFLD should be carefully assessed for underlying sleep disorders that may not only have a negative impact on their health but also on the health related quality of life.

AUTHORS CONTRIBUTION

Heshaam M. Mir, MD: Study concept, data interpretation, manuscript writing and editing.

Maria Stepanova PhD: Study concept, data analysis, manuscript editing.

Hena Afendy: Study concept, data interpretation, manuscript editing.

Rebecca Cable: Study concept, data interpretation, manuscript editing.

Zobair M. Younossi MD, MPH: Study concept, data interpretation, manuscript writing and editing (This author is the guarantor of the entire manuscript).

CONFLICTS OF INTEREST

All authors have none to declare.

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