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Are Hypothyroidism and Obstructive Sleep Apnea Independent Risk Factors for the Development of Non-Alcoholic Fatty Liver Disease?

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Abstract

Background: Non-Alcoholic Fatty Liver Disease (NAFLD) is defined as the accumulation of fat in the liver so that it weighs more than 5% of the total liver weight. Over the past decade, there has been growing evidence in regard to the association between NAFLD/NASH and both thyroid dysfunction and OSA.

Design/Method: A retrospective analysis was performed using the National Inpatient Sample (NIS) database for 2010. The variables included in this study were identified using ICD9 codes for 2010. A Case-Control design was used to compare the cohorts. A binary and multiple logistic regression statistical tests were used to examine the prevalence and the relative risk of having NASH among people with hypothyroidism and OSA. IBM SPSS Statistics for Windows.

Results: Approximately 32,000 patients with NASH and randomly selected 28,000 without NASH were identified for the study. Within the NASH group, 4,097 (11%) were found to have coexisting hypothyroidism, and 4,213 (12.7%) patients of the Non-NASH group had hypothyroidism. Patients with hypothyroid disease has almost the same probability of having NASH compared to individuals without hypothyroidism (crude odds ratio is 1.1, adjusted odd ratio is 0.7, CI 95%, P=0.00). In the Nash group, 937 (2.5%) were found to have OSA, whereas (1.25%) 383 patients only have OSA in the Non-Nash group. People with obstructive sleep apnea have 2.3 higher probabilities to have NASH than people without history of sleep apnea (crude odd ratio is 2.3, adjusted odd ratio is 1.72, P=0.00, CI 95%).

Conclusion: People with obstructive sleep apnea are almost two times more likely to have NAFLD than people without obstructive sleep apnea. On the other hand, Hypothyroidism was not found to be a risk for NAFLD.

Keywords: Obstructive sleep apnea; Hypothyroid; Non-alcoholic fatty liver disease

Introduction

Non-Alcoholic Fatty Liver Disease (NAFLD) is defined as the accumulation of fat in the liver so that it weighs more than 5% of the total liver weight. There should be no background of heavy alcohol consumption or secondary hepatic accumulation of lipids to make the diagnosis of NAFLD [1]. NAFLD is classified into nonalcoholic fatty liver, in which there are no signs of inflammation and into Non-Alcoholic Steato Hepatitis (NASH) in which signs of inflammation are present, along with the ballooning of the hepatocytes on microscopy. NAFLD may progress to fibrosis and further progression results in cirrhosis, making NAFLD the most common cause of cryptogenic cirrhosis [1,2].

The prevalence of NAFLD has increased in the last two decades from 5.51% in 1988 to 11.01% in 1994 [3]. The reported prevalence of NAFLD in the world is estimated to range between 2.8% to 46%, while the prevalence of NASH ranges between 3% to 5% [4,5]. In the United States, the prevalence has varied across studies and is estimated to range from 10% to 46% depending on the population and definition used in each of the studies [3,5,6]. Several studies showed that the prevalence of NAFLD varies among ethnicity with the highest prevalence noted in the Hispanic population and the least found among African Americans [3,7,8]. The recent rise in prevalence of NAFLD has been associated with the increase in the prevalence of the risk factors for NAFLD including central obesity, type 2 diabetes mellitus, dyslipidemia, and metabolic syndrome. Although many studies examined the correlation between the aforementioned conditions and NAFLD, there are other factors like hypothyroidism, Obstructive Sleep Apnea (OSA), and hypogondasim whose relationships with NAFLD have yet to be well established [9].

Over the past decade, there has been growing evidence in regard to the association between NAFLD/NASH and both thyroid dysfunction and OSA [10-12]. The thyroid gland secretes thyroxin hormone, which regulates cell metabolism, the expenditure of energy, and distributes fat throughout the body. The slow metabolism experienced in hypothyroidism increases adipogenesis and weight gain, both of which are well known risk factors for NAFLD [13].

OSA is another risk factor that may play a role in NAFLD pathogenesis. The estimated prevalence of OSA in North America is approximately 20% to 30% in males and 10% to 15% in females [14]. NASH and OSA share obesity as a common risk factor. The prevalence of OSA progressively increases as the Body Mass Index (BMI) increases [10,15,16]. However, a direct relation between OSA as an

independent risk factor for NASH has not been well established. Several cross-sectional studies have examined the correlation of elevated liver enzymes with NASH but, most of these studies lacked a control group and the elevation in the liver enzymes was not enough evidence to support the diagnosis of NASH.

In our study, we examined if hypothyroidism and OSA are independent risk factors for the development of NASH.

Design/Method

We performed a retrospective analysis using the National Inpatient Sample (NIS) database for 2010. The NIS is a database and software tool developed for the Healthcare Cost and Utilization Project (HCUP). The NIS is the largest publicly available inpatient health care database in the United States. It contains data from more than 7 million hospital stays each year. Weighted, it estimates more than 35 million hospitalizations nationally. Admissions for the 2010 NIS totaled over 7 million.

The variables included in this study were identified using ICD9 codes for 2010. ICD9 Codes (5718), (2449) and (327.23) identified NAFLD, hypothyroidism and OSA respectively. Once patients with NAFLD were identified, an equal number of non-NAFLD patients were randomly selected out of the 7 million admissions. A Case-Control design was used to compare the cohorts. A binary logistic regression statistical test was used to examine the prevalence and the relative risk for having NASH in people with hypothyroidism and OSA. IBM SPSS Statistics for Windows, Version 19.0 was used to execute the analysis. A Confidence Interval (CI) of 95% and P value less than 0.05 were determined to define significance.

Results

Approximately 32,000 patients with NASH and randomly selected 28,000 without NASH were identified for the study. Table 1 demonstrates their characteristics. Within the NASH group, 4,097 (11%) were found to have coexisting hypothyroidism, and 4,213 (12.7%) patients of the Non-NASH group had hypothyroidism (Table 2). Patients with hypothyroid disease has almost the same probability of having NASH compared to individuals without hypothyroidism (crude odds ratio is 1.1, adjusted odd ratio is 0.7, CI 95%, P=0.00) (Table 3).

	Non-NASH Patients	NASH Patients
Race		
White	24,526 (84%)	23,447 (71%)
Black	19,73 (6.8%)	3,106 (9.4%)
Hispanic	15,87 (5.4%)	4,675 (14.2%)
Asian	294 (1%)	647 (1.9%)
Native American	136 (0.5%)	225 (0.7%)
Others	605 (2.1%)	906 (2.7%)
Sex		
Male	12,688 (38%)	15,634 (42%)
Female	20,442 (62%)	21,189 (56%)

Table 1: Characteristics of patient population.

	Non-NASH Patients	NASH Patients	Total
No Hypothyroidism	28,954	32,736	61,690
Hypothyroidism	4,213	4,097	8,310
Total	33,167	36,833	70,000

Table 2: Prevalence of Hypothyroidism in NASH and Non-NASH patients.

Diseases	Crude odd ratio	Adjusted odd ratio
Hypothyroid	1.1	0.7
DM	2.7	2.3
HTN	1.5	1.2
Sleep apnea	2.2	1.7

Table 3: Prevalence of diseases in odd ratios (crude/adjusted).

In the NASH group, 937 (2.5%) were found to have OSA, whereas 383 (1.25%) patients only have OSA in the Non-NASH group (Table 4). People with obstructive sleep apnea have 2.3 higher probabilities to have NASH than people without history of sleep apnea (crude odd ratio is 2.3, adjusted odd ratio is 1.72, P=0.00, CI 95%) (Table 3).

	Non-NASH Patients	NASH Patients	Total
No OSA	32,784	35,896	68,680
OSA	383 (1.2%)	937 (2.5%)	1,320
Total	33,167	36,833	70,000

Table 4: Prevalence of OSA in NASH and Non-NASH patients.

As far as other associated comorbidities, 31% of NASH patient group had diabetes and 69% did not. 53.9% had HTN and 46.1% did not. 27.1% of the NASH population was obese while 72.9% were not (Tables 5-8).

	Non-NASH Patients	NASH Patients	Total
No Diabetes	28,528	25,398	53,926
Diabetes	4,639	11,435	16,074
Total	33,167	36,833	70,000

Table 5: Prevalence of Diabetes Mellitus in NASH and Non-NASH patients.

	Non-NASH Patients	NASH Patients	Total
No HTN	18,710	16,979	35,689
HTN	14,457	19,854	34,311

Total	33,167	36,833	70,000

Table 6: Prevalence of Hypertension (HTN) in NASH and Non-NASH patients.

	Non-NASH Patients	NASH Patients	Total
Not Obese	30,449	26,841	57,290
Obese	2,718	9,992	12,710
Total	33,167	36,833	70,000

Table 7: Prevalence of Obesity in NASH and Non-NASH patients.

	Non-NASH	NASH Patients
CHF	31,470 (94%)	4,901 (94.8%).
Non CHF	1,697 (5.1%)	1,932 (5.2%).
Total	33,167	36,833

Table 8: Prevalence of CHF in NASH and Non- NASH patient.

Obese patients were 4 times more likely to have NASH than non-obese people. (Crude odd ratio 4.1, adjusted odd ration 3.6, CI (3.9-4.3), P value of 0.00). Diabetic individuals were about 3 times more likely to have NASH than non-diabetic (crude Odd ratio of 2.7, adjusted odd ratio 2.3, CI 2.6-2.8, P value of 0.00) (Table 3).

Discussion

While the correlation of obesity, hypertension, hyperlipidemia, and glucose intolerance with NASH have all been well studied with multiple published papers supporting their correlation, more studies are needed to further understand the association of hypothyroidism and OSA [3,17,18].

Liangpunsakul and Chalasani [12] examined the correlation of hypothyroidism and NASH in a case-control design which showed that there was a higher number of hypothyroid patients in NASH patient population than in the Non-NASH cohort (OR: 2.3, 95% CI: 1.2-4.2, P=0.008). Another study done by Pagadala et al. [19] also supported the correlation between hypothyroidism and NASH with his larger population size of 246 cases and 430 controls of a biopsy proven NASH. This finding remained statistically significant after adjusting for other variables including age, diabetes, dyslipidemia and hypertension, but not gender [16]. A systemic review executed by Eshraghian and Jahromi [20] showed that the prevalence of hypothyroidism is around 15.2% to 36.3% among patients with NAFLD/NASH. Our study found that the probability of having NASH in people with hypothyroidism was less likely than in those without hypothyroidism (CI: 08-0.9 odd ratio 0.7 and P=0.000). This finding contradicts previous studies and serves to call to question the previous association of hypothyroidism as a risk factor for NASH/NAFLD.

OSA and NASH share a common risk factor of obesity. Sharing this risk factor makes studying the correlation between OSA and NASH confounding. The pathogenesis of obesity causing OSA is well studied. Yet, the correlation between OSA and NASH is still under investigation. Jun et al. [21] hypothesized that intermittent hypoxia may lead to NASH by up-regulating Reactive Oxygen Species (ROS) generation via the NADPH oxidase system. Drager et al. [22] reported that NAFLD progresses to NASH in the OSA patients by the activation of the inflammatory cascades and cytokines. In the presence of obesity and hepatic steatosis, intermittent hypoxia in patients with OSA increased mRNA production and protein levels of pro-inflammatory cytokines which hypothetically increases the speed of fibrosis. Kheirandish-Gozal et al. [23] in their case-control study including 376 children with OSA, found an increase in liver enzymes levels that are frequently found in obese, snoring children, particularly among those with OSA and/or metabolic dysfunction. Effective treatment of OSA resulted in improved liver function test in the vast majority of these patients. Overall, evidence that OSA has an independent effect on liver enzyme levels remains inconclusive and the diagnosis of NASH cannot base on liver enzymes elevation only.

In our case-control cohort study, there was statistical difference in the prevalence of OSA among people with NASH as compared to people without NASH (CI: 1.9-2.3, crude odds ratio: 2.3, and adjusted odd ration 1.7 and P value of 0.00).

Some limitations of this study stem from the NIS database used, as it tracks admissions, not necessarily patients. It also looks at patients that are hospitalized and therefore does not accurately reflect the healthy, generalized population. There is also clerical error involved as the database is taken from charts completed by humans, with human error, as well as completion of charts from many different institutions across the United States. These variables are expected in a sample size of this magnitude. To offset some of these limitations, we used the same database for looking at the associations of diabetes mellitus, hypertension, and obesity with NASH. Our data supported the generally accepted conclusion that all three are risk factors for NASH, thereby giving more validity to the data we present on hypothyroidism and OSA.

Conclusion

Our study used a very large nationwide database and found that there is no strong association between hypothyroidism and NASH. Our study also showed that, when obesity is adjusted in the risk assessment, there is still association between OSA and NASH. Further studies need to be performed in order to fully define these relationships, but this study's large population size has helped to question the assumed associations of hypothyroidism and OSA in patients with NASH by contradicting for the hypothyroidism patients and goes along with previous finding of OSA and NASH from previous studies but in a largest data that has been study so far.

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