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NONALCOHOLIC FATTY LIVER DISEASE AND RISK OF INCIDENT HYPERTENSION: A SYSTEMATIC REVIEW

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Abstract

NAFL, or Non-Alcoholic Fatty liver, is a disorder characterized by the presence of steatosis; steatosis, an inflammation and expansion of liver cells with or without liver fibrosis (NASH, Non-Alcoholic Steatohepatosis); and cirrhosis. If more fibrosis or cirrhosis develops, the potential risk of liver cancer will grow. Current epidemiological research indicates that around 49.5% of people with hypertension also have NAFLD. In addition, the prevalence of hypertension is significantly higher in patients with NAFLD than in the general population. It has been proven that both the presence of NAFLD and the severity of the illness are significantly associated with higher risks of a broad spectrum of extrahepatic effects, including cardiovascular disease (CVD) and type 2 diabetes mellitus. Hypertension is a disorder characterized by multiple medical issues. In the majority of patients, the pathophysiological cause is unknown (essential or primary). Primary hypertension is incurable but can be managed. Another group with a low percentage has a unique cause, which is known as secondary hypertension. Endogenous and exogenous causes of secondary hypertension are numerous. If the source of secondary hypertension can be discovered, these patients' hypertension may be curable. All studies demonstrate that persons with NAFLD are more likely to have hypertension than those without NAFLD.

Keyword: *Cardiovascular disease; Hypertension; Inflammation; Insulin resistance; Nonalcoholic fatty liver disease (NAFLD)*

INTRODUCTION

NAFLD includes a histopathological spectrum in the form of NAFL or Non-Alcoholic Fatty liver, a condition where steatosis is found; steatosis, an inflammation and enlargement of liver cells with or without liver fibrosis (NASH), Non-Alcoholic Steatohepatosis), and cirrhosis. If there is further fibrosis or cirrhosis, then the possible risk of liver malignancy will increase.[1] The prevalence of NAFLD has shown an increasing trend over the last few decades, and the global prevalence of NAFLD has been estimated at 25%. In a systematic review and meta-analysis by Younossi et all, the Middle East had the highest prevalence (32%) followed by South America (30%), Asia (27%), North America (24%), Europe (24%), and Africa (13%).[2]

Approximately 20-86/1000 people use ultrasound examination and 34/1000 people with H-MRS a study followed 11448 subjects for 5 years, 12% of cases of NAFLD diagnosed by ultrasonography.[34] There are significant differences in the number of reports on the prevalence of NAFLD cases in the general population. A meta-analysis study estimated that 25.24% of NAFLD cases worldwide were diagnosed using imaging.[5] In Asia, the prevalence of NAFLD is estimated to be around 27.37% with 63.45% of them being found to be NASH. Research by Hasan I et al shows that the prevalence of NAFLD in Indonesia is 30%.[6]

In fact, according to a meta-analysis conducted by Li et al. in 2019, the prevalence of NAFLD in Asia has increased from 25% between 1995 and 2005 to 34% between 2012 and 2017. Among the subregions of Asia, Southeast Asia will have the greatest prevalence of NAFLD at 42%. Indonesia is the nation with the greatest prevalence of NAFLD at 51%. The prevalence of hypertension, a multifactorial condition that is caused by the interaction between a person's genetic predisposition and the risk factors in their environment, is increasing and is currently affecting approximately thirty percent of the general population.[7,8]

Recent research from the field of epidemiology has shown that around 49.5% of patients diagnosed with hypertension also have NAFLD. Furthermore, the prevalence of hypertension is much higher in individuals diagnosed with NAFLD than it is in the general population. It has been demonstrated that both the existence of NAFLD and the severity of the condition are substantially connected with increased risks of a wide range of extrahepatic consequences, such as cardiovascular disease (CVD) and type 2 diabetes mellitus.[9–11]This article does some research on whether or not there is a connection between nonalcoholic fatty liver disease (NAFLD) and incident hypertension.

METHODS

For data collection, processing, and reporting, this study adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 project guidelines. The regulations that were adopted were based on these considerations. This review of the literature seeks to establish a link between nonalcoholic fatty liver disease (NAFLD) and the risk of incident hypertension. The following are the primary concerns raised by the current investigation: 1) Articles must always be written in English and must emphasize the risk of incident hypertension and nonalcoholic fatty liver disease (NAFLD). 2) This review looked at articles published after 2015 but before the time frame of this systematic review. The anthology will not include editorials, submissions without a DOI, reviews of previously published articles, or entries that are substantially identical to those in the journal.

The search for studies to be included in the systematic review was carried out from March, 19th 2023 using the PubMed and SagePub databases by inputting the words: “nonalcoholic fatty liver disease” and “hypertension”. Where *("non alcoholic fatty liver disease"[MeSH Terms] OR ("non alcoholic"[All Fields] AND "fatty"[All Fields] AND "liver"[All Fields] AND "disease"[All Fields]) OR "non alcoholic fatty liver disease"[All Fields] OR ("nonalcoholic"[All Fields] AND "fatty"[All Fields] AND "liver"[All Fields] AND "disease"[All Fields]) OR "nonalcoholic fatty liver disease"[All Fields]) AND ("hypertense"[All Fields] OR "hypertension"[MeSH Terms] OR "hypertension"[All Fields] OR "hypertension s"[All Fields] OR "hypertensions"[All Fields] OR "hypertensive"[All Fields] OR "hypertensive s"[All Fields] OR "hypertensives"[All Fields])* is used as search keywords.

Abstract and title of each study were utilized to assess eligibility. So, historical literature serves as their primary source. After examining numerous papers with the same results, submissions in unpublished English are requested. The systematic review included only studies that met the inclusion criteria. This restricts search results to those meeting the provided criteria. Evaluation is next. Authors, publishing dates, location, activities, and parameters were listed in the study's analysis. After saving search results in EndNote, the database was purged of duplicate articles. Relevance of each paper's title and abstract was evaluated by two reviewers.

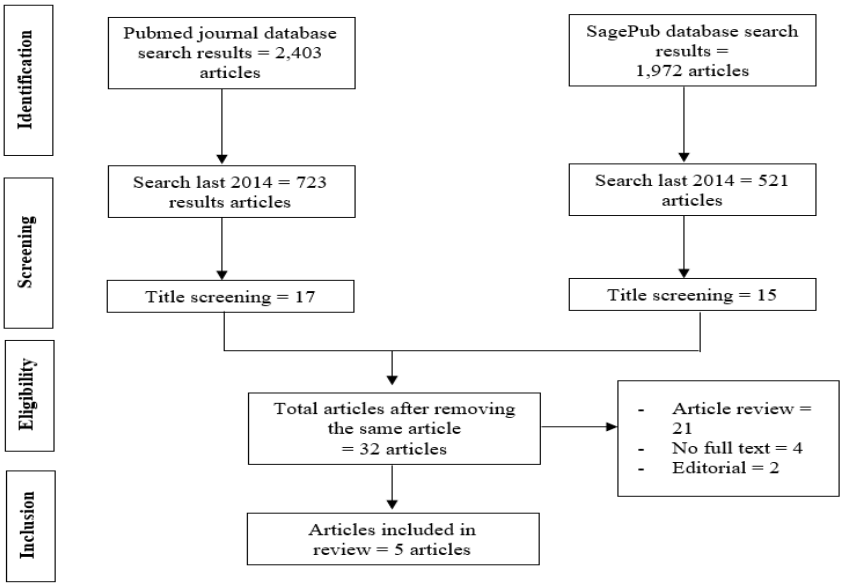


Figure 1. Article search flowchart

Each author read the title and abstract of each paper before deciding which to study. Following that, we'll go over all of the publications that meet the review's inclusion criteria. Following our research, we will review relevant research publications. This rule selects manuscripts for review. It should be easier to select items for further investigation. Which previous studies were included in the review, and why were they included?

RESULT

Bonnet, et al (2017)[12] showed the number of people with high blood pressure went up in all four groups of baseline GGT and alanine aminotransferase. After taking into account sex, age, waist circumference, fasting glucose, smoking, and alcohol use, only GGT was significantly linked to incident hypertension (standardized odds ratio [sOR = 1.21; 95% confidence interval [CI] = 1.10-1.34; P <0.0001). Changes in GGT levels during the follow-up were also linked to an increased risk of high blood pressure, even when body weight didn't change. In the multivariable model, hypertension was more likely to happen if the FLI was looked at as a continuous value or if it was at least 60 at the start. In the RISC cohort, the hepatic insulin resistance index was linked to the risk of developing high blood pressure within three years (sOR = 1.54 [1.07–2.22]; P = 0.02).

A study condected by Sung, et al (2014)[13] with 911 individuals acquired incident hypertension. In 1418 patients, incident fatty liver developed during follow-up, whereas in 684 patients, baseline fatty liver cleared throughout follow-up. Even after adjusting for various variables, incident fatty liver was linked with incident hypertension (aOR = 1.60 [95% CI = 1.30-1.96]; p <0.001). This link was only marginally decreased by further adjustment for the change in body mass index between baseline and follow-up (aOR = 1.36 [95% CI = 1.10-1.60]; p = 0.004). After resolution of fatty liver at follow-up, the risk of incident hypertension was not significantly different from the reference group (aOR = 1.21 [95% CI: 0.90-1.40]; p = 0.20).

Table 1. The litelature include in this study

Author	Origin	Method	Sample	Conclusion
Bonnet, 2017[12]	France	Prospective study	2,565 data drom medical resord	It was found that having a higher GGT and FLI at the beginning of the study, as well as a rise in GGT throughout time, increased the likelihood of incident hypertension. Increased hepatic insulin resistance was a risk factor for developing hypertension and may be a connection between liver indicators and hypertension.
Sung, 2014[13]	Republic of Korea	Retrospective cohort study	11,448 patients	A higher baseline risk of hypertension is seen in those who have a history of incident fatty liver disease.
Aneni, 2015[14]	United State of America (USA)	Cross sectional study	5362 healthy middle-aged men and women	Even in the absence of other metabolic risk factors, prevalent NAFLD may be identified early on in the development of hypertension. This is because hypertension is a metabolic disease. If a patient is hypertensive but not obese, controlling their blood pressure may be helpful in preventing or minimizing the development of NAFLD.
Ryoo, 2014[15]	Republic of Korea	Prospective cohort study		When compared to a normal or milder condition of NAFLD, a more advanced state has a greater propensity to be related with the development of hypertension. In addition to this, NAFLD was found to be a contributing factor in the development of hypertension.
Zhou, 2018[16]	China	Cohort prospective study	Four thousand six hundred eighty-six subjects (3177 males and 1509 females)	The FLI's assessment of nonalcoholic fatty liver was able to predict independently whether or not the Chinese population would develop hypertension.

Aneni, et al (2015)[14] showed NAFLD was prevalent at a rate of 36.2%. Individuals with NAFLD were older (mean age of 46 versus 42, P <0.001) and had a higher BMI (mean BMI of 29 versus 24.7 kg/m2, P <0.001). In those with normal

BP, PHT, and HTN, the prevalence of NAFLD was 16.5, 37.5, and 59.3%, respectively. In multivariate analyses, PHT and HTN were associated with increased risks of NAFLD (PHT-adjusted odds ratio [aOR] = 1.3, 95% CI = 1.1–1.6; HTN-aOR =1.8, 95% CI =1.4–2.3) relative to normal BP. In nonobese hypertensive patients, BP management (BP <140/90 mmHg) was independently linked with a 40% reduction in the risks of NAFLD prevalence. Normotensive persons and prehypertensive patients were more likely to have a low fibrosis risk than hypertension patients (FIB-4 ≥1.3). Ryo, et al (2014)[15] showed the prevalence of hypertension increased with NAFLD severity (normal: 14.4%, mild: 21.8%, moderate to severe: 30.1%, P 0.001). Even after adjusting for other multiple covariates, the hazard ratios (95% confidence intervals) for hypertension were higher in the mild group (1.07; 1.00–1.15) and moderate to severe group (1.14; 1.00–1.30), compared with normal group, respectively (P for trend <0.001). : Development of hypertension is more potentially associated with the more progressive NAFLD than normal or milder state. In addition, NAFLD was an independent risk factor for hypertension.

Other study condtucted with four thousand six hundred eighty-six participants (3177 males and 1509 females) were tracked for nine years. The subjects were separated into distinct groups based on the fatty liver index. Using univariate and multivariate Cox regression models, the risk variables for hypertension were analyzed. Following nine years of observation, 2,047 patients developed hypertension. The cumulative incidence of hypertension over nine years was 43.7%, ranging from 36.0% (FLI <30) to 75.3% (FLI ≥60) (P <0.001). Cox regression studies revealed that nonalcoholic fatty liver, as measured by the fatty liver index, was positively and independently related to the probability of incident hypertension. FLI's ROC AUC was 0.701% (95% CI = 0.686-0.716], which was greater than that of its components.[16]

DISCUSSION

The prevalence of hypertension increases with age and is a major risk factor for cerebro-cardiovascular disease and has an important impact on quality of life. The Writing Group of the American Society of Hypertension defines hypertension as a cardiovascular syndrome caused by a number of interrelated factors. Therefore, a comprehensive evaluation is needed involving the cardiovascular system and other risk factors. In the global population, the prevalence of hypertension is 26.4% which is expected to increase to one third of the population by 2025.[17]

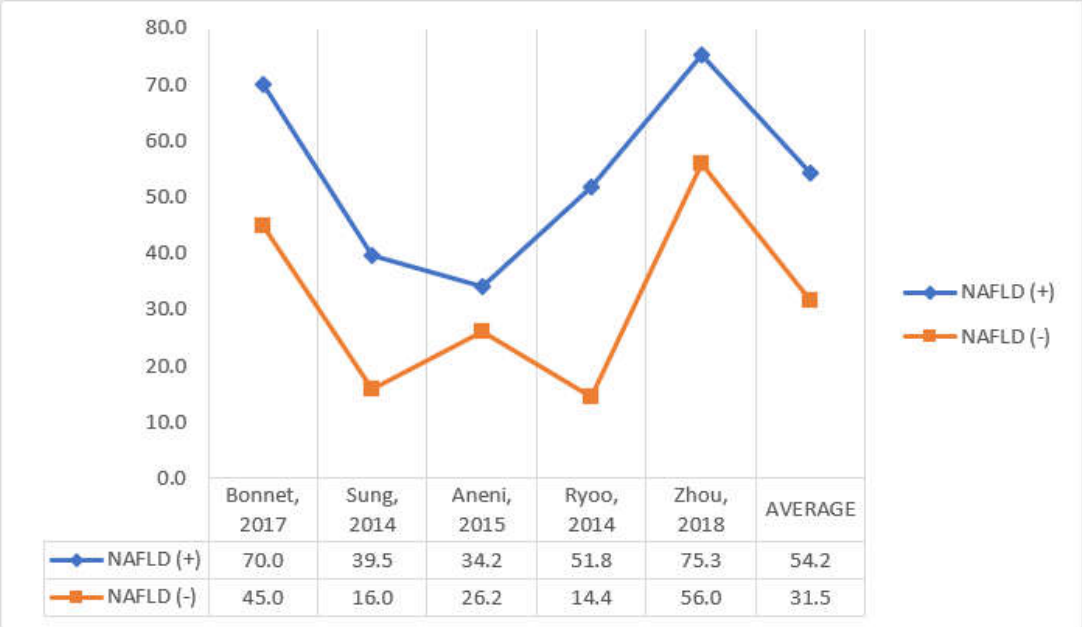
Hypertension is a disease with various medical conditions. In most patients the pathophysiological etiology is unknown (essential or primary). Primary hypertension cannot be cured but can be controlled. Another group of the population with a low percentage has a special cause, known as secondary hypertension. There are many causes of secondary hypertension; endogenous or exogenous. If the cause of secondary hypertension can be identified, the hypertension in these patients can potentially be cured.[7,18]

Bonnet, et al (2017)[12] demonstrated before that elevated GGT activity is associated with an increased risk of cardiovascular disease in the general population. The strength of the association between GGT and incident hypertension was highlighted by the fact that it persisted after excluding individuals with GGT levels above the normal range and those who did not consume alcohol or consumed little (5 g/day) at baseline in the D.E.S.I.R. cohort, indicating that the association is not attributable to individuals with high GGT activity and/or elevated alcohol consumption.[19]

In cross-sectional research, hypertensive persons have a higher prevalence of NAFLD than those with normal blood pressure. A new study in a Korean population indicates that the development of fatty liver is connected with an increased risk of hypertension throughout a 5-year follow-up period. In addition, ultrasonography has demonstrated a correlation between the degree of NAFLD and the risk of incident hypertension in Korean men. They extended these findings by demonstrating that a fatty liver, as measured by a high FLI, was also predictive of incident hypertension in a white cohort, independent of age, sex, and alcohol consumption.[13,20,21]

The discovery that the increase in FLI across the follow-up period was linked with the risk of hypertension lends credence to the possibility of a pathophysiological connection between liver fat accumulation and the development of high blood pressure. Confirmation of the association between fatty liver and hypertension risk, however, will require additional research with a more precise measurement of intrahepatic fat content. Beyond the presence of increased liver fat content, our study supports a novel role for hepatic insulin resistance in the development of elevated BP, and to our knowledge, is the first to investigate this relationship.[14,15,21]

Nonobese people with NAFLD have a higher risk of nonalcoholic steatohepatitis, hepatic fibrosis, and abnormal liver enzymes than obese people with NAFLD. A recent study found that nonobese NAFLD is associated with a significantly higher risk of mortality than obese NAFLD. As a result, nonobese people with NAFLD are in a relatively high-risk group. The current NAFLD management guidelines recommend losing weight through diet, physical activity, or both. These interventions result in blood pressure control, which may explain why blood pressure control without regard to weight or metabolic risk factors did not confer protection from NAFLD in the general population.[14,22]



	Bonnet, 2017	Sung, 2014	Aneni, 2015	Ryoo, 2014	Zhou, 2018	AVERAGE
NAFLD (+)	70.0	39.5	34.2	51.8	75.3	54.2
NAFLD (-)	45.0	16.0	26.2	14.4	56.0	31.5

Figure 2. Comparison of the incidence of hypertension in patients with NAFLD and without NAFLD

One possible explanation for their findings is that insulin resistance played a role in the phenomenon. Insulin resistance is recognized as a significant risk factor in the onset and progression of NAFLD. Studies have demonstrated that those with NAFLD have a higher baseline insulin resistance compared to people with normal liver function. Insulin resistance is also the proven risk factor of CVD by inducing the dyslipidemia and secreting proinflammatory cytokine, such as tumor necrosis factor-α and interleukin-6 accelerating the arteriosclerosis.[15,23]

Because of the consequences of insulin resistance, there is a possibility that arterial vascular elasticity and luminal width would diminish, which will lead to an increase in blood pressure. In addition, sympathetic activation, which was likely a contributor to the development of hypertension, was brought on by insulin resistance. Recent research has demonstrated that insulin resistance can cause an increase in blood pressure by stimulating the sympathetic nervous system. [15,23]

CONCLUSION

All of the research come to the same conclusion, which is that people who have NAFLD have a much higher prevalence of hypertension compared to those who do not have NAFLD.

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