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NONALCOHOLIC FATTY LIVER DISEASE AND ALBUMINURIA : A SYSTEMATIC REVIEW

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Abstract

Background: *The presence of fat storage in the liver that is larger than 5% of the liver's weight is diagnostic of nonalcoholic fatty liver disease (NAFLD), which can occur in the absence of excessive alcohol consumption or a secondary cause of liver illnesses. It is interesting to note that it has been hypothesised that NAFLD might be able to contribute to albuminuria by exacerbating the endothelial dysfunction that results from systemic inflammation.*

Aim: *This article examines the link between nonalcoholic fatty liver disease and albuminuria.*

Methods: *This study showed that it met all of the requirements by looking at the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines. So, the experts could make sure that the study was as current as possible. The search method used a number of electronic reference databases, such as Pubmed and SagePub, to look for papers that were published between 2000 and 2023. We didn't look at review papers, articles that had already been published, or articles that were only half done.*

Result: *In the PubMed database, the results of our search brought up 89 articles, whereas the results of our search on SagePub brought up 33 articles. The results of the search conducted for the last year of 2013 yielded a total of 22 articles for PubMed and 16 articles for SagePub. In the end, we compiled a total of 17 papers, 12 of which came from PubMed and five of which came from SagePub. We included seven research that met the criteria.*

Conclusion: *Study has consistently shown that there is a correlation between NAFLD and albuminuria.*

Keyword: *Albuminuria; Kidney disease; Nonalcoholic fatty liver disease (NAFLD)*

INTRODUCTION

The presence of fat storage in the liver that is larger than 5% of the liver's weight is diagnostic of nonalcoholic fatty liver disease (NAFLD), which can occur in the absence of excessive alcohol consumption or a secondary cause of liver illnesses.[1,2] A prior study found that the prevalence of NAFLD over the world (as detected by ultrasonography) is less than 25 percent. The pathophysiology of NAFLD is intricately connected to insulin resistance as well as persistent inflammation, and NAFLD is frequently regarded as the liver manifestation of metabolic syndrome.[3,4]

It is estimated that more than 60 million persons in the United States are afflicted with NAFLD. This coincides with an increase in global obesity rates. Obesity, diabetes mellitus, hypertension, hyperuricemia, and a lack of regular physical activity are all known to increase the likelihood of developing NAFLD.[5] Albuminuria, retinopathy, and peripheral neuropathy are all microvascular consequences of diabetes mellitus that have been linked to NAFLD. It has also been established that NAFLD is connected with diabetic nephropathy.[4,6,7]

Microalbuminuria, which was defined as a urine albumin-to-creatinine ratio of 30–300 mg/g, has been shown to be connected not only with chronic kidney disease (CKD), but also early cardiovascular mortality in patients with or without diabetes or hypertension.[8] This was found to be the case in individuals whose microalbuminuria had a urinary albumin-to-creatinine ratio of 30–300 mg/g. Recent studies have proposed that early detection and treatment of albuminuria in general populations can help prevent cardiovascular and renal illness.[9]

It is interesting to note that it has been hypothesised that NAFLD might be able to contribute to albuminuria by exacerbating the endothelial dysfunction that results from systemic inflammation.[9,10] In addition, findings from recent studies have revealed that NAFLD may be a risk factor for albuminuria in patients who are diabetic as well as those who do not have diabetes; however, the outcomes of these investigations have been inconsistent.[3,8,11] We will discuss nonalcoholic fatty liver disease (NAFLD) as well as albuminuria throughout the course of this essay.

METHODS

The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 checklist was used as the basis for the establishment of the criteria that were used to oversee the process of carrying out this systematic review. These standards were utilised to ensure that all of the relevant information was collected and analysed. Articles on "nonalcoholic fatty liver disease and albuminuria" were the topic of this systematic review that was designed to research them. This review was designed to investigate them. These are the many aspects of the topics that were looked into during the research that is being considered right now.

The following conditions need to be fulfilled in advance in order for your work to be taken into consideration: 1) Articles have to be written in English; 2) Articles have to be able to be read online in their entirety; and 3) Articles had to have been published after 2013, but before this systematic evaluation was carried out. Under no circumstances will any of the following types of written submissions be considered for inclusion in the anthology: 1) Editorial letters, 2) submissions that do not have a DOI linked with them, and 3) article reviews and submissions that are comparable to one another.

The search for papers to be included in the systematic review began on July 17th, 2022 using the PubMed and SagePub databases with the search terms on "nonalcoholic fatty liver disease" and "albuminuria" 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 ("albuminuria"[MeSH Terms] OR "albuminuria"[All Fields])) AND ((y_10[Filter]) AND (clinicaltrial[Filter] OR randomizedcontrolledtrial[Filter]))* is used as search keywords.

After conducting a literature analysis and looking at the titles and abstracts of previously published studies, the author of the study revised the criteria for what should be included in the study and what should not be included in the study. These changes were made after the author considered what should not be included in the study. During the process of developing the systematic review that we carried out, we gave any and all consideration to only those research studies that were able to satisfy each and every one of our standards. Each study's title, author, publication date, study origin location, research study design, and research variables are all bits of information that can be gathered during the collection process.

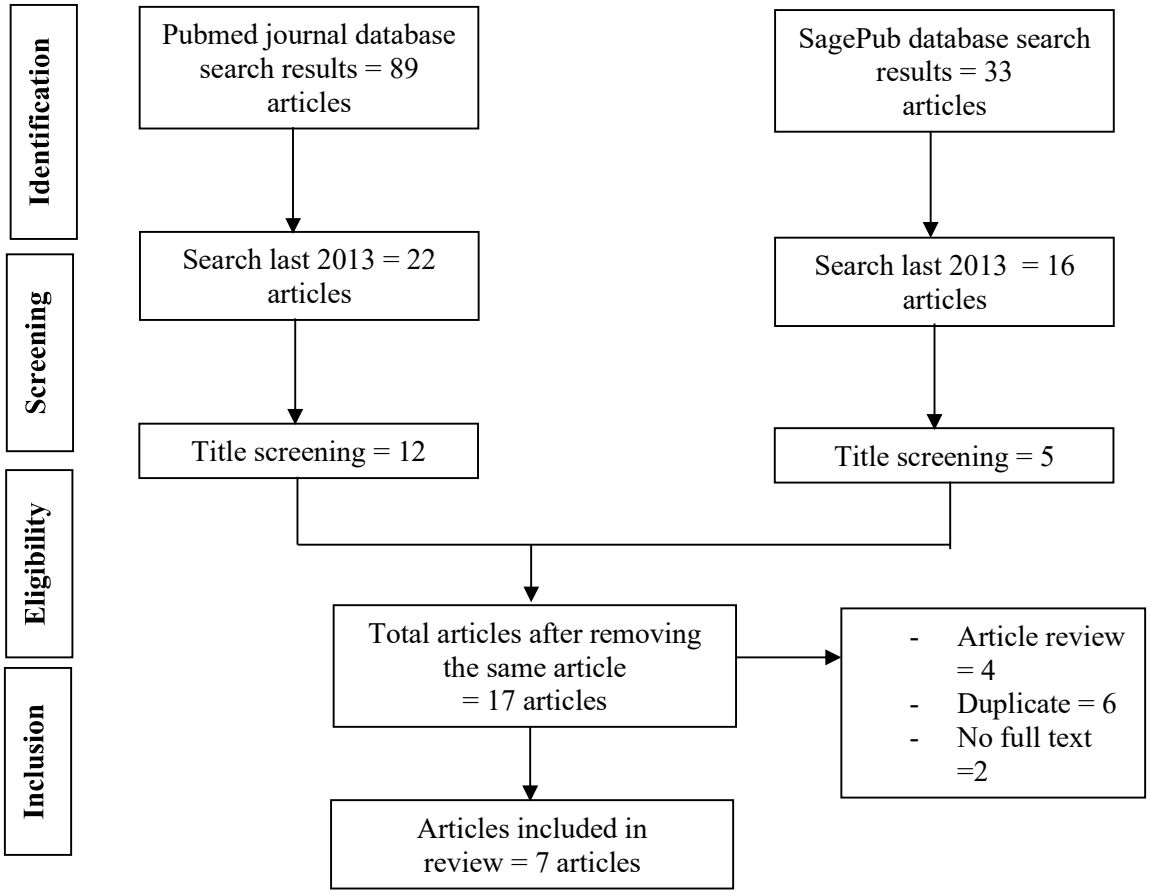

Figure 1. Article search flowchart

The writers did their own independent evaluations on a selection of the research that was given in the titles and abstracts of the publications in order to determine which studies ought to be taken into consideration. This allowed them to choose which studies ought to be taken into consideration. They were able to identify, as a result of this, which studies should be taken into consideration. The next thing that needs to be done is a study of the full texts of the studies that can be included in the systematic review since they fulfil the requirements. The objective of this analysis is to ascertain whether or not certain pieces of research may be pertinent to the goals of the review. This will be done so that the evaluation is as comprehensive as it possibly can be. This is the goal.

RESULT

In the PubMed database, the results of our search brought up 89 articles, whereas the results of our search on SagePub brought up 33 articles. The results of the search conducted for the last year of 2013 yielded a total of 22 articles for PubMed and 16 articles for SagePub. In the end, we compiled a total of 17 papers, 12 of which came from PubMed and five of which came from SagePub. We included seven research that met the criteria.

Han, et al (2022)[12] showed 16.1 % subjects were classified as having albuminuria. Subjects with NAFLD exhibited a higher rate of albuminuria than subjects without NAFLD (crude odds ratios [ORs] = 2.60–2.95, all $P < 0.001$). Regardless of hypertension, insulin resistance, or obesity, the risk for albuminuria was higher in the NAFLD group than in the group without NAFLD (measured by either FLI or LFS; all $P < 0.001$). When subjects with NAFLD had sarcopenia, the risk of albuminuria further increased (OR = 4.33–4.64, all $P < 0.001$). Multiple logistic regression analyses also demonstrated that NAFLD was independently associated with albuminuria (OR = 2.58, 95 % confidence interval [CI] = 1.66–4.02, $P < 0.001$ for FLI, OR = 1.87, 95 % CI = 1.28–2.75, $P = 0.001$ for LFS).

Kang, et al (2019)[13] showed the urinary albumin/creatinine ratio in the non-NAFLD and NAFLD groups was 3.05 ± 0.14 and 5.19 ± 0.42, respectively ($P < 0.001$). The correlation coefficients between the fatty liver index and urinary albumin/creatinine ratio were 0.124 in the Pearson's correlation test and 0.084 in the partial correlation test ($P < 0.001$ and $P = 0.002$). Linear regression analysis showed a positive association between the fatty liver index and the urinary albumin/creatinine ratio on multivariate analysis. Logistic regression analysis showed that the odds ratio for low-grade albuminuria with NAFLD was 2.31 (95% CI = 1.47-3.61; $P < 0.001$) on the multivariate analysis. Subgroup analyses according to the presence of metabolic syndrome or age showed that the association between NAFLD and the urinary albumin/creatinine ratio was stronger for participants without metabolic syndrome and in those aged < 50 years.

Choi, et al (2018)[14] showed participants in higher quintiles of log-FLI were more obese and hypertensive and had greater glycemic exposure, poorer lipid profiles, and greater increases in log-UACR compared with lower quintiles. Linear

regression analysis demonstrated that log-FLI was associated with systolic and diastolic blood pressure, body mass index, waist circumference, fasting plasma glucose, glycated hemoglobin, and log-UACR. In logistic regression adjusted for age, sex, body mass index, waist circumference, and fasting plasma glucose, the odds ratio (OR) of microalbuminuria was elevated in quintile 1 (adjusted OR [aOR] = 2.161, 95% CI = 0.453–10.31) and quintile 5 (aOR = 6.387, 95% CI = 1.317–51.58), when compared to quintile 2.

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Result
Han, 2022[12]	Republic of Korea	Cross sectional study	1,795 participants	Within the general population of Korea, having NAFLD was found to be related with an elevated risk of albuminuria. This connection was seen even in participants with sarcopenia, despite the fact that hypertension, insulin resistance, chronic renal disease, diabetes, and obesity were all present.
Kang, 2019[13]	Republic of Korea	Cross sectional study	3,867 participants	In this particular investigation, NAFLD was found to be related with low-grade albuminuria in male participants who did not have diabetes.
Choi, 2018[14]	Republic of Korea	Cross sectional study	1,605 participants	It would appear that there is a correlation in the form of a J between fatty liver index (FLI) and urine albumin/creatinine ratio (UACR) in the general population that is healthy.
Heidari, 2017[15]	Iran	Cross sectional study	255 patients with T2DM	Patients diagnosed with type 2 diabetes have a very high risk of developing NAFLD. The NAFLD is not regarded to be a risk factor for diabetic nephropathy.
Kasapoglu, 2016[16]	Turkey	Cross sectional study	479 cases	Microalbuminuria was shown to be more prevalent among NAFLD patients compared with control cases, and this prevalence was found to be rising with the advanced stages of NAFLD, despite the fact that the two primary etiologic factors of microalbuminuria, type 2 diabetes and obesity, were ruled out. Our findings suggest that NAFLD cases are more likely to have microalbuminuria than control cases.
Jenks, 2014	United Kingdom	Cross sectional study	933 subject	In group of older persons with Type 2 diabetes, the prevalence of hepatic steatosis or non-alcoholic fatty liver disease was not related with a deterioration in renal function throughout a 4-year follow-up period.
Hamdy, 2013[17]	Kingdom of Saudi Arabia	Cross sectional study	1,150 patients	The nonalcoholic fatty liver disease was found to be the strongest predictor of cardiovascular and renal impairment by logistic regression analysis.

Heidari, et al (2017)[15] showed NAFLD was present in 86.66 percent of these 221 individuals. 33% of all persons were found to have diabetic nephropathy, 32% of all individuals were found to have microalbuminuria, and 10% of all individuals were found to have macroalbuminuria. It was found that having diabetes for a longer period of time, having a higher Body Mass Index (BMI), having hypertriglyceridemia, and having a higher HbA1c were all substantially linked with having NAFLD. In patients who had type 2 diabetes, diabetic nephropathy was also substantially related with the length of time they had diabetes and their HbA1c levels.

Kasapoglu, et al (2016)[16] conducted a study with ultrasound findings grouped subjects 37.9% instances without liver fat were the control group. However, severe nonalcoholic fatty liver disease (NAFLD) had a statistically greater urine protein/creatinine ratio than the other three groups. Microalbuminuria was statistically higher in moderate and severe NAFLD than in controls and mild NAFLD. According to multiple logistic regression study, fatty liver disease raised microalbuminuria risk by 1.87 times irrespective of BMI and HOMA-IR.

Jenks, et al (2014)[18] showed hepatic steatosis nor non-alcoholic fatty liver disease were significantly associated with rate of decline in renal function, with the mean rate of decline in estimated glomerular filtration rate being –1.55 ml/min/1.73 m per year for participants with hepatic steatosis compared with –1.84 ml/min/1.73 m for those without steatosis (P = 0.19). Similar results were obtained when the analysis was restricted to participants with and without non-alcoholic fatty

liver disease (–1.44 vs. –1.64 ml/min/1.73 m per year, respectively; P = 0.44). Additionally, neither hepatic steatosis nor non-alcoholic fatty liver disease were associated with the onset or regression of albuminuria during follow-up (all P ≥ 0.05).

Hamdy, et al (2013)[17] showed only 62.25% patients completed the follow-up examination and were included in the final analysis. 35.8% of them fulfilled the sonographic criteria of NAFLD. The frequency of cardiovascular accident and renal impairment was significantly higher in them 50.7% vs. 23% (P < 0.001) for cardiovascular events, 32.8% vs. 18.4% (P < 0.001) for microalbuminuria; and 8.9% vs. 2.9%, (P < 0.001) for macroalbuminuria. Also, mean estimated glomerular filtration rate (eGFR) was significantly lower in patients with NAFLD (96 ± 23.28 vs. 111 ± 28.37; P < 0.001).

DISCUSSION

Research has consistently shown that there is a correlation between NAFLD and albuminuria. 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.[19] The increasing prevalence of NAFLD in Asia can largely be attributed to dietary and lifestyle changes driven by rapid economic growth and urbanization. A meta-analysis of 237 studies by Li et al, 2019 found that the prevalence of NAFLD in Asia is 29.62% which is almost 50.9 cases per 1000 people per year.[20]

Multisystemic NAFLD affects extrahepatic organs. NAFLD often causes CVD, type 2 diabetes, metabolic syndrome, extrahepatic malignancy, CKD, hypothyroidism, PCOS, and psoriasis. NAFLD increases CKD risk regardless of cardiorenal risk factors such obesity, hypertension, or type 2 diabetes, according to several studies. In systematic reviews and meta-analyses, NAFLD severity increases the risk and severity of CKD in diabetics and non-diabetics, even after controlling for CKD risk variables. NAFLD patients also had a higher incidence of albuminuria, which may lead to CKD, according to a meta-analysis.[21] The possibility of a link between NAFLD and renal illness is an intriguing idea; nevertheless, there is no evidence to conclusively establish a cause-and-effect relationship, and the connection is complicated.[22,23]

A number of the risk factors for NAFLD and renal disease are the same. These include metabolic abnormalities and inflammation. However, these studies defined chronic kidney disease based solely on the eGFR and/or urine dipstick test results for overt proteinuria.[24] Previous studies have suggested that NAFLD can lead to chronic kidney disease through dyslipidemia, hypertension, insulin resistance, chronic inflammation, or oxidative stress; however, these studies defined chronic kidney disease based solely on the eGFR. The presence of obvious proteinuria as well as a decline in eGFR are both indicators of a more advanced stage of chronic renal disease.[22]

A number of research concentrated on the connection between NAFLD and microalbuminuria. Patients with type 2 diabetes were enrolled in the study and the researchers demonstrated that there was a positive connection between NAFLD and microalbuminuria. However, diabetes mellitus itself is a significant risk factor for albuminuria as well as DM-specific renal diseases. These include glomerular vasculopathy and hyperfiltration, both of which might cause misunderstanding regarding the independent relationship between NAFLD and albuminuria in patients who have diabetes. As a result, excluding patients who had diabetes from the study could make it easier to establish a connection that is independent of the two variables.[22,23]

Historically, a UACR of less than 30 mg/g has been considered to be normal. On the other hand, the degree of albuminuria has been shown to positively correlate with adverse outcomes.[21] When employing a single cut-off point, it is difficult to definitively differentiate individuals whose ratios are below a cut-off value from those whose ratios are beyond the cut-off point. As a result, the cutoff point of UACR less than 30 mg/g being related with bad outcomes is not an absolute value. Recent research have shown that participants with LGA 17-20 had an increased risk of unfavourable outcomes.[12,16,25]

The overall frequency of low-grade albuminuria (LGA) in the general population, regardless of the presence or absence of comorbidities, is higher than the prevalence of micro-albuminuria or overt proteinuria. In addition, the appearance of LGA occurs at an earlier stage of renal impairment than the manifestation of micro-albuminuria or overt proteinuria. Therefore, early detection and intervention of LGA would be more beneficial in preventing the advancement of chronic renal disease or other diseases. This is because early detection of LGA would allow for more time for treatment.[12,16,25]

Lin et al. looked at the link between LGA and NAFLD in a Chinese population and found some interesting results. According to their research, a positive association exists between NAFLD and LGA, and their study also found that this association is stronger in men and/or younger populations than it is in women and/or older populations. In addition, there was not a significant difference between the two factors when looking at patients who had diabetes. However, their data could not entirely eliminate people who had hepatitis B and did not take into account chronic conditions such cerebrovascular accidents or coronary artery disease, both of which would be factors that could confuse the results of the UACR.[26]

Using laboratory results such as hepatitis B surface antigen or anti-HCV antibody, our data fully excluded individuals with hepatitis B and C. However, patients with cerebrovascular accidents or coronary artery disease were included in the study. Similar findings emerged from both our investigation and the one carried out by Lin et al. It was shown that there were significant differences in young people as well as participants who did not have MetS, which suggested that the relationship between NAFLD and LGA was stronger in participants who did not have MetS at the same time.[12,20]

CONCLUSION

Study has consistently shown that there is a correlation between NAFLD and albuminuria.

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