

NONALCOHOLIC FATTY LIVER DISEASE AND ALBUMINURIA : A SYSTEMATIC REVIEW

Amandha Rizky Taufika^{1*}, Alvita Niamullah¹

¹Sondosia Regional General Hospital, Bima Regency, Indonesia

***Corresponding Author:**

amandharizky1289@gmail.com

Abstract

Background: Non-alcoholic fatty liver disease (NAFLD) is associated with the dysregulation of multiple metabolic and inflammatory pathways. These can lead to extrahepatic disorders involving the kidney, a vulnerable organ responsible for extra-renal complications. Evaluating the association between NAFLD and low-grade albuminuria as a renal complication would be helpful to better understand the pathophysiology and extra-hepatic complications of NAFLD.

The aim: This study aims to show incidence, correlation of nonalcoholic fatty liver disease and albuminuria

Methods: By comparing itself to the standards set by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, this study was able to show that it met all of the requirements. So, the experts were able to make sure that the study was as up-to-date as it was possible to be. For this search approach, publications that came out between 2013 and 2023 were taken into account. Several different online reference sources, like Pubmed and SagePub, were used to do this. It was decided not to take into account review pieces, works that had already been published, or works that were only half done.

Result: Non-alcoholic fatty liver disease (NAFLD) is associated with the dysregulation of multiple metabolic and inflammatory pathways. These can lead to extrahepatic disorders involving the kidney, a vulnerable organ responsible for extra-renal complications. Evaluating the association between NAFLD and low-grade albuminuria as a renal complication would be helpful to better understand the pathophysiology and extra-hepatic complications of NAFLD.

Conclusion: Understanding the incidence, correlation of nonalcoholic fatty liver disease and albuminuria

Keyword: Nonalcoholic fatty liver disease, Albuminuria, Incidence, Correlation

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is the most common etiology of chronic liver disease, affecting approximately 25% of the adult population worldwide. NAFLD is a complication of obesity, and some patients are thought to progress to nonalcoholic steatohepatitis (NASH), which is characterized histologically by the presence of steatosis, inflammation, and hepatocellular ballooning with or without fibrosis, ultimately leading to cirrhosis, hepatocellular carcinoma (HCC), and death.^{1,2}

One of the unique characteristics of hepatocytes, which function as protein secretion factories, is that they synthesize high levels of various basic blood proteins such as albumin, transferrin, and lipoproteins. Thus, due to their active anabolic and metabolic states, hepatocytes have a large size ranging from 20 to 30 μm , and are rich in different organelles. It has been reported that the contacts between mitochondria and other organelles such as the endoplasmic reticulum (ER) and lipid droplets (LDs) directly contribute to cellular lipid metabolism and energy homeostasis. However, not all subcellular structures involved in mitochondrial homeostasis have been clearly identified, particularly hepatocytes-specific organelles.³

Albumin is the most abundant plasma protein and plays a key role in the regulation of plasma colloid osmotic pressure. It also has various other physiologic functions, including solubilization, binding, and transport of endogenous and exogenous molecules; antioxidative, anti-inflammatory, and hemostatic effects; endothelial stabilization; and adjustment of capillary permeability. Importantly, albumin is a major prognostic factor in patients with liver cirrhosis, being reported as a significant predictor of death in over 100 studies.⁴ Hypoalbuminemia is frequently observed in patients with advanced cirrhosis and is generally defined as an intravascular albumin level $< 3.5 \text{ g/dL}$.⁵

Human serum albumin (HSA) is the most abundant protein in healthy individuals and it plays an important role in maintaining plasma colloid osmotic pressure. It has been shown that albumin infusion can improve the prognosis of patients with spontaneous peritonitis or hepatorenal syndrome, not only *via* plasma volume expansion, but also because of its non-colloid osmotic function. However, the clinical significance of the non-oncotic functions of HSA has not been investigated in detail. It is likely that albumin function is altered during liver dysfunction, and recent studies have shown that the three-dimensional structure of albumin is modified, along with its function, in liver diseases, and that these modifications are related to the specific clinical features and severity of the disease, and the prognosis.⁶

Recently, accumulating studies have revealed numerous membrane-less organelles that are formed *via* protein phase separation and transition. Biomacromolecules phase separate or transit to form subcellular high-concentrated complexes, enabling increased rates of biochemical reactions (transcription, signal transduction, autophagy, LD fusion, etc.) or storing relevant RNA and proteins. Moreover, it has also been reported that phase separation into quinary assemblies is a survival strategy for organisms under stressful conditions. Thus, these organelles often acquire new functions in unexpected ways, which inspired us to explore novel organelles within hepatocytes that provide protection under lipotoxic pressure. Since the intracellular concentration of a protein is one of the key prerequisites for phase separation and transition, we focused on albumin, which is expressed at the highest level among all hepatic-specific proteins.³

METHODS

Protocol

By following the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the author of this study made certain that it was up to par with the requirements. This is done to ensure that the conclusions drawn from the inquiry are accurate.

Criteria for Eligibility

For the purpose of this literature review, we compare and contrast the incidence and correlation between non alcoholic fatty liver disease and albumin. This is done to provide an explanation and improve the handling of non alcoholic fatty liver disease. As the main purpose of this paper, to show the relevance of the difficulties that have been identified as a whole.

In order for researchers to take part in the study, it was necessary for them to fulfil the following requirements: 1) The paper needs to be written in English. In order for the manuscript to be considered for publication, it needs to meet both of these requirements. 2) The studied papers include several that were published after 2013, but before the time period that this systematic review deems to be relevant. Examples of studies that are not permitted include editorials, submissions that do not have a DOI, review articles that have already been published, and entries that are essentially identical to journal papers that have already been published.

Search Strategy

We used "nonalcoholic fatty liver disease"; "NAFLD and albuminuria" as keywords. The search for studies to be included in the systematic review was carried out using the PubMed and SagePub databases by inputting the words: ("*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]) OR "*nonalcoholic fatty liver*"[All Fields] AND ("*albumin s*"[All Fields] OR "*albumine*"[All Fields] OR "*albumines*"[All Fields] OR "*albumins*"[MeSH Terms] OR "*albumins*"[All Fields] OR

"albumin"[All Fields]) AND ((ferritin[Filter]) AND (clinicaltrial[Filter]) AND (2013:2023[pdat])) used in searching the literature.

Data retrieval

After reading the abstract and the title of each study, the writers performed an examination to determine whether or not the study satisfied the inclusion criteria. The writers then decided which previous research they wanted to utilise as sources for their article and selected those studies. After looking at a number of different research, which all seemed to point to the same trend, this conclusion was drawn. All submissions need to be written in English and can't have been seen anywhere else.

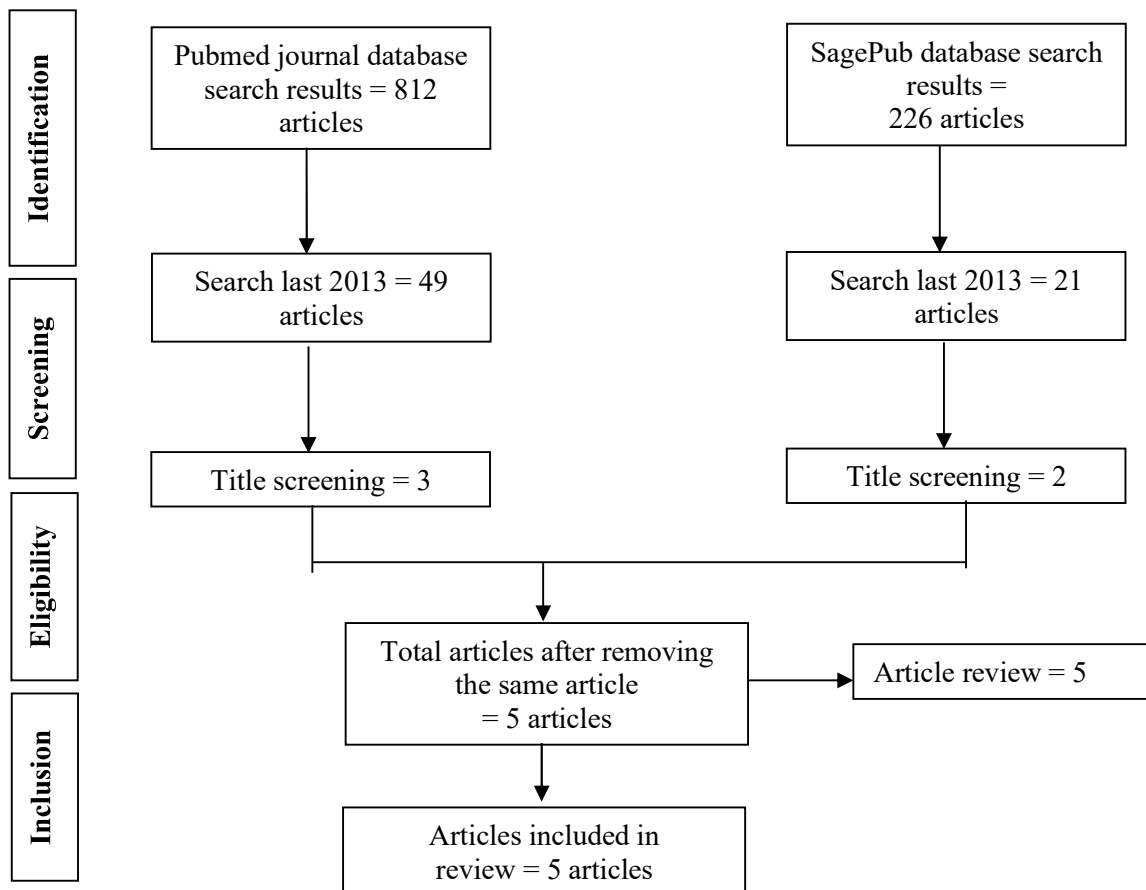


Figure 1. Article search flowchart

Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

Quality Assessment and Data Synthesis

Each author did their own study on the research that was included in the publication's title and abstract before making a decision about which publications to explore further. The next step will be to evaluate all of the articles that are suitable for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review depending on the findings that we've uncovered. This criteria is utilised in the process of selecting papers for further assessment. In order to simplify the process as much as feasible when selecting papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

RESULT

In the PubMed database, the results of our search brought up 812 articles, whereas the results of our search on SagePub brought up 226 articles. The results of the search conducted for the last year of 2013 yielded a total 49 articles for PubMed and 21 articles for SagePub. In the end, we compiled a total of 5 papers, 3 of which came from PubMed and 1 of which came from SagePub. We included five research that met the criteria.

Abbate, et al⁷ (2021) showed that hepatic iron load, fasting insulin, serum ferritin, and platelets were associated with mean albuminuria independently of gender, age, diabetes, HbA1c, stages of NAFLD, and presence of liver fibrosis. Increased hepatic and body stores of iron have been linked to increased risk of metabolic complications and progression of hepatic

and cardiovascular disease, among others. Excessive iron might play a direct effect on insulin resistance, and the DIOS condition J. Clin. Med. 2021, 10, 3187 14 of 18 may accelerate the evolution to T2DM, cardiovascular disease, and liver disease. In turn, excessive iron might further expose patients with confirmed NAFLD to other metabolic complications such as increased albuminuria.

Qin, et al⁸ (2022) showed that patients with T2DM and NAFLD frequently have albuminuria, which is associated with a higher risk of significant steatosis. Additionally, we showed that the level of urinary ACR was associated with an increased hepatic steatosis burden in NAFLD patients. Hepatic complication should be kept in mind in T2DM patients with albuminuria. Further studies with a larger number of patients and longer periods of observation, along with liver biopsy, are needed to elucidate the association more clearly between albuminuria occurrence and NAFLD progression.

Table 1. The literature include in this study

Author	Origin	Method	Sample	Result
Abbate et al, 2021 ⁷	USA	Retrospective cohort study	75 patients	UACR correlated with NAFLD, HepFe, triglycerides, serum ferritin, fasting insulin, insulin resistance (calculated using the homeostatic model assessment for insulin resistance—HOMA-IR-formula), and platelets ($p < 0.05$). Multiple regression analysis adjusted for gender, age, eGFR, HbA1c, T2DM, and stages of NAFLD, found that HepFe ($p = 0.02$), serum ferritin ($p = 0.04$), fasting insulin ($p = 0.049$), and platelets ($p = 0.009$) were associated with UACR ($R^2 = 0.370$; $p = 0.007$). UACR, liver fat accumulation, serum ferritin, and HOMA-IR increased across stages of HepFe ($p < 0.05$). Patients with severe NAFLD presented higher HepFe, fasting insulin, HOMA-IR, and systolic blood pressure as compared to patients in NAFLD stage 1 ($p < 0.05$).
Qin et al, 2022 ⁸	USA	Cross Sectional study	36.463 patients	A total of 36,463 individuals were included in our analysis; 9.56% participants were categorized as having albuminuria overall and increased with the higher SII tertiles (tertile 1, 7.83%; tertile 2, 8.49%; tertile 3, 12.13%; p for trend 0.05).
Kawaguchi et al, 2021 ⁹	Japan	Retrospective study	229 patients	Data related to liver fibrosis progression, albumin, and prothrombin time were significantly associated with the occurrence of serious complications associated with cirrhosis. We compared 22 event and 133 nonevent cases of chronological changes in the data per year and found that serum albumin concentration was significantly lower in the group that developed serious complications (event cases: -0.21 g/dL/year, nonevent cases: -0.04 g/dL/year ($P < .001$)). This albumin decline was only the associated factor with the event incidence by multivariate analysis ($P < .01$).
Kang et al, 2019 ¹⁰	Korea	Cross sectional study	3867 patients	In the multivariate analysis, 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 $P = 0.002$, respectively). 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% confidence interval, 1.47-3.61; $P < 0.001$) on the multivariate analysis.
Sheng et al, 2021 ¹¹	China	Cohort study	10.749 patients	The average age of the study population was 43.65 ± 15.15 years old. During the 5-year follow-up, 1860 non-obese subjects had NAFLD events. In the Cox multiple regression model, after adjusting the model according to important risk factors, the AAPR and NAFLD risk were independently correlated, and with a gradual increase in the AAPR, the NAFLD risk decreased gradually (HR: 0.61, 95% CI: 0.47, 0.81; P-trend < 0.0001). Additionally, there were significant interactions between the AAPR and BMI, blood pressure and lipids (P-interaction < 0.05). Stratified analysis showed that the risk of AAPR-related NAFLD decreased in people with normal blood pressure and lipid levels, while the risk of AAPR-related NAFLD increased abnormally in people who were underweight.

Kawaguchi, et al⁹(2021) showed that decline in serum albumin over a clinical course of several years following a diagnosis of NAFLD is an important factor associated with the incidence of severe events. These results highlight the importance of careful monitoring of changes in serum albumin concentration for predicting the occurrence and prognosis of severe events in advanced NAFLD/NASH.

Kang, et al¹⁰ (2019) showed that NAFLD was associated with low-grade albuminuria in men without diabetes mellitus in this study. Therefore, men with a relatively high fatty liver index or NAFLD should be closely monitored for low-grade albuminuria, especially in absence of metabolic syndrome.

Sheng, et al¹¹ (2021) showed provides the first evidence that the AAPR is an independent predictor of future NAFLD events in non-obese people. For non-obese people with a low AAPR, especially those with BMI < 18.5 kg/m², more attention should be given to the management of risk factors for NAFLD to prevent future NAFLD.

DISCUSSION

Non-alcoholic fatty liver disease (NAFLD) is chronic liver disease; encompassing conditions ranging from fatty liver disease to liver cirrhosis. NAFLD is characterized by fat accumulation without competing etiologies for steatosis such as viral hepatitis or heavy alcohol intake. Primary NAFLD is typically associated with metabolic disturbances, such as metabolic syndrome (MetS) and/or insulin resistance, in particular. Previous epidemiologic studies have shown that the prevalence of NAFLD is approximately 30% in the USA, 24% in Europe, and 27% in Asia. The prevalence of NAFLD is rapidly increasing. Previous studies have shown a positive association between NAFLD and systemic chronic diseases, such as diabetes mellitus (DM), cardiovascular disease, sarcopenia, and osteoporosis, through various metabolic disturbances.¹⁰

Albumin is the most abundant plasma protein and albumin infusion is commonly used. Conventionally, the biologic and therapeutic effects of albumin have been thought to be due to its oncotic properties. However, albumin has a variety of biologic functions, including molecular transport, anti-oxidation, anti-inflammation, endothelial stabilisation, anti-thrombotic effects, and the adjustment of capillary permeability. Despite this, the functions of albumin have not been thoroughly investigated. Recent studies have shown non-alcoholic fatty liver disease (NAFLD), viral hepatitis, cirrhosis, and liver failure to be associated with impairments in albumin function, which are associated with impairments in liver function and disease prognosis. Post-translational modifications of albumin cause structural modifications that affect protein function. Recently, the concentration of albumin associated with normal function, the 'efficient albumin concentration', has been attracting more interest. In addition, although many biologic markers, including albumin concentration, are widely used for the assessment of early liver dysfunction in patients with liver diseases, the predictive values are unsatisfactory.⁶

Albuminuria is a well-known risk factor of cardiovascular disease and chronic kidney disease progression. Microalbuminuria is classically defined by an albumin level of 30-300 mg/day in the urine or a urinary albumin/creatinine ratio (UACR) of 30-300 mg/g. However, considering the limitation of single cut-off values, researchers have focused on the importance of high levels of albuminuria of < 30 mg/day (or 30 mg/g); this condition has been called "low-grade albuminuria" (LGA). Previous studies have shown an association between LGA and various cardiometabolic diseases. Tanaka et al. demonstrated that LGA leads to high mortality rates.¹⁰

NAFLD is associated with the dysregulation of multiple metabolic and inflammatory pathways (e.g., peripheral/hepatic insulin resistance, chronic inflammation, oxidative stress, or the renin-angiotensin system). These can lead to extrahepatic disorders such as DM, hypertension, MetS, or cardiovascular disease. Epidemiologic or experimental studies have shown an association between NAFLD and extrahepatic disorders as a consequence of these pathophysiological disorders. The kidney is an organ influenced by extra-renal complications and is vulnerable to different cardio-metabolic disturbances induced by NAFLD.¹⁰

NAFLD is one of the emerging forms of CLD that is yet to be fully investigated to clarify the clinical and pathological features in detail. Currently, the established pathological feature of NAFLD is steatosis, which is the accumulation of lipid, primarily triglyceride, in hepatocytes. NAFLD can also be complicated by obesity, DM, HL, HT, and hyperuricemia in many patients.¹²

NAFLD is a sexual dimorphic disease, in which premenopausal women have a lower prevalence of NAFLD compared to men or postmenopausal women. Carulli et al. evaluated difference in patients with NAFLD according to sex and showed that men with NAFLD were on an average 10 years younger than women with NAFLD. They suggested that physiological levels of estrogen might be protective for the development of NAFLD due to the improvement in insulin sensitivity, dyslipidemia, and visceral fat accumulation. Postmenopausal women have a higher risk of NAFLD compared to premenopausal women, and the risk of NAFLD in these women was comparable to that of men. In addition, hormone replacement therapy was associated with a decreased risk of NAFLD after menopause.¹⁰

Some studies have focused on the association between NAFLD and microalbuminuria. Casoinic et al. enrolled patients with type 2 DM and showed there was a positive association between NAFLD and microalbuminuria. However, DM per se is a strong risk factor for albuminuria and DM-specific renal pathologies, such as glomerular vasculopathy or hyperfiltration, which may lead to confusion regarding the independent association between NAFLD and albuminuria in patients with DM.¹⁰

A UACR of < 30 mg/g has classically been defined as normal. However, the amount of albuminuria is positively correlated with poor outcomes. It is difficult to definitely distinguish participants with ratios below a cut-off value using a single cut-off point from those above. Therefore, the threshold of UACR \geq 30 mg/g associated with adverse outcomes is not absolute. Recent studies have demonstrated adverse outcomes in participants with LGA. The prevalence of LGA in the general population with or without comorbidities is greater than that of micro-albuminuria or overt proteinuria. In addition, LGA presents at an earlier stage of renal damage than micro-albuminuria or overt proteinuria. Therefore, early detection and intervention of LGA would be more effective in the prevention of the progression of chronic kidney disease or other pathologies.¹⁰

CONCLUSION

NAFLD is one of the emerging forms of CLD that is yet to be fully investigated to clarify the clinical and pathological features in detail. Currently, the established pathological feature of NAFLD is steatosis, which is the accumulation of lipid, primarily triglyceride, in hepatocytes. NAFLD can also be complicated by obesity, DM, HL, HT, and hyperuricemia in many patients. Although these metabolic syndrome-associated conditions in NAFLD patients can be treated, the therapeutic benefit in CLD is uncertain. A significantly increased risk of albuminuria among patients with NAFLD was observed in this systematic review. Physicians should pay more attention to the early detection of individuals with microalbuminuria especially in patients with NAFLD.

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