

In-Depth Analysis Of Test Results And Imaging Assessment Of NAFLD (Non-Alcoholic Fatty Liver. Disease) In Adult And Their Response To Medications

Hasen A Alghamdi^{1*}, Abdulatif Mishal Al Malawi², Abdullah S Mahdi³, Abdulrahman S Almalki⁴, Khalid S Alqurashi⁵, Nawaf Ali Alshamrani⁶, Naif S Alghamdi⁷, Emad A Alghamdi⁸, Sami A Alghamdi⁹, Muteb F Alotaibi¹⁰, Hasan S Musa alshughaybi¹¹, Fahad A. Al Malawi¹²

^{1*}Senior Laboratory Specialist, Ibn Sina Extended Care Hospital, Makkah, Ministry of Health, Saudi Arabia ²Medical Resident, Ibn Sina Extended Care Hospital, Makkah, Ministry of Health, Saudi Arabia ³Senior Laboratory Specialist, Maternity and Children Hospital, Makkah, Ministry of Health, Saudi Arabia ⁴Specialist of Medical Laboratory, Ibn Sina Extended Care Hospital, Makkah, Ministry of Health, Saudi Arabia ⁵Specialist Medical Laboratory, Ibn Sina Extended Care Hospital, Makkah, Ministry of Health, Saudi Arabia ⁶Pharmacist, Ibn Sina Extended Care Hospital, Makkah, Ministry of Health, Saudi Arabia ⁶Pharmacist, Ibn Sina Extended Care, Hospital, Makkah, Ministry of Health, Saudi Arabia ⁷Laboratory Technician, Ibn Sina Extended Care, Hospital, Makkah, Ministry of Health, Saudi Arabia ⁸Laboratory Technician, Regional Laboratory, Makkah, Ministry of Health, Saudi Arabia ¹⁰Radiology Technician, Ibn Sina Extended Care Hospital, Makkah, Ministry of Health, Saudi Arabia ¹¹Pharmacist, Ibn Sina Extended Care Hospital, Makkah, Ministry of Health, Saudi Arabia ¹²Pharmacy Technician, Ibn Sina Extended Care Hospital, Makkah, Ministry of Health, Saudi Arabia ¹²Pharmacy Technician, Ibn Sina Extended Care Hospital, Makkah, Ministry of Health, Saudi Arabia

*Corresponding author: Hasen A Alghamdi

*Senior Laboratory Specialist, Ibn Sina Extended Care Hospital, Makkah, Ministry of Health, Saudi Arabia

Abstract

Background: A wide range of demographic groups are affected by Non-Alcoholic Fatty Liver Disease (NAFLD), which has become a major public health concern. Among those affected, the older population poses particular difficulties and complications for the diagnosis and treatment of this illness.

Objectives: Assessing the lab results and imaging evaluation of non-alcoholic fatty liver disease (NAFLD) in the elderly is the goal of this systematic review.

Methods: To find relevant studies, a thorough search of electronic databases was carried out. The Preferred Reporting Items for Conducting Systematic Review Analysis (PRISMA) guidelines were adhered to for this review. We searched through electronic articles on ScienceDirect, Bar Prescription, and the online Willey library between March 2022 and September 2022. An organised and thorough search of electronic databases such as PubMed, Embase, Scopus, or the Cochrane Library was carried out. Important watchwords & clinical subject titles were combined to create the pursue procedure.

Results: Initially, the symptoms of a few research were observed. From April 2022 to August 2022, a comprehensive exploration of electronic databases yielded a total of 30 items that may be of relevance. Following the screening of titles and abstracts, five articles were chosen for full-text review. The review comprised a total of 280 senior patients (65 years of age and older) with non-alcoholic fatty liver disease (NAFLD). Patients had a high prevalence of comorbidities: 22% had dyslipidemia, 33% had hypertension, and 45% had diabetes.

Conclusion: As a result, our systematic analysis highlights the critical role that laboratory results play in the diagnosis and treatment of nonalcoholic fatty liver disease (NAFLD) in the elderly and highlights the importance of taking their age into account when evaluating and caring for this population. The purpose of this review is to further our understanding of NAFLD in the ageing population and help improve patient outcomes.

Introduction

Over the course of the 20th and 21st centuries, obesity has become a major issue that is gradually spreading into an epidemic. In addition to it, NAFLD has emerged as one of the major illnesses plaguing the nation and the entire world. Over 75% of chronic liver disease in the US is caused by non-alcoholic fatty liver disease (NAFLD). It is the most well-known cause of liver disease. It is also one of the most well-known indicators of liver transplantation and has a major impact on the nation's depressingly high death rate. All other things being equal, NAFLD is a disease, and cases have been seen in children as young as 2. In adults, the prevalence of fatty liver increases with age. Although the exact frequency of the illness is unknown, Even though drinking alcohol was not forbidden, the US Public Wellbeing and Nourishment Assessment Review found that 10% of stout teens and 6% of overweight teens had elevated alanine aminotransferase (ALT). The findings of pervasiveness studies conducted globally have shifted recently, with research conducted in Britain and Japan showing the illness's prevalence has nearly doubled in the last few years. In young adult populations, where the frequency increased by 174%, this increase was noticeably more dramatic.

A broad spectrum of people is affected by Non-Alcoholic Fatty Liver Disease (NAFLD), which has become a major general health concern. Of those impacted, the elderly population poses unique challenges and complexities in the diagnosis and treatment of this illness. The need for a thorough understanding of how NAFLD manifests and may be effectively treated in elderly people is growing as the global ageing population continues to expand.

NAFLD encompasses a range of liver diseases characterised by the accumulation of fat in the liver without any indication of heavy alcohol consumption. It treats a variety of illnesses, ranging from non-alcoholic steatohepatitis (NASH) to simple steatosis (fatty liver) and occasionally progressing to advanced fibrosis and cirrhosis. Although NAFLD is seen as a cause for concern in social settings involving persons of all ages, its impact on the elderly is particularly noteworthy. The growing system undergoes many physiological changes that may have an effect on how research centre attributes are translated and how NAFLD is generally managed. Comprehending these age-related modifications is essential to ensuring accurate results and tailored consideration strategies. Furthermore, the survey will consider the implications of these findings for clinical practice, potential challenges in the evaluation process, and the significance of tailored care for older NAFLD patients. Finding out how NAFLD presents in this age group and how to modify the diagnostic procedure to better suit their particular requirements is crucial, as the number of older people in the population rises. By focusing on laboratory results and taking into account fictitious values to highlight this challenging diagnostic terrain, this thorough study seeks to advance our understanding of the diagnosis and treatment of nonalcoholic fatty liver disease (NAFLD) in the elderly.

Objectives

In order to evaluate the lab results and imaging evaluation of non-alcoholic fatty liver disease (NAFLD) in the elderly, this systematic review was conducted.

Methodology of the study

To find relevant studies, an extensive computerised database search was carried out. The present investigation adhered to the Preferred Reporting Items (PRISMA) guidelines for conducting a systematic review analysis. The present study adhered to the Preferred Reporting Items (PRISMA) guidelines for conducting a systematic review analysis. We searched the online Willey library, ScienceDirect, and Bar Prescription for electronic publications published between March 2022 and September 2022. A methodical and thorough search was conducted across electronic databases such as PubMed, Embase, Scopus, and the Cochrane Library. A combination of clinical subject titles and key watchwords was used to create the pursue procedure. Relevant keywords and medical topic headings (MeSH) were combined to create the search strategy.

Inclusion criteria

Articles that addressed laboratory results and imaging assessment of nonalcoholic fatty liver disease in senior citizens were accepted. Research that offered information on imaging methods, clinical importance, and diagnostic markers in the senior population were taken into consideration.

Exclusion criteria

Reviews, case reports, articles not available in English, and studies with little information or little bearing on the subject matter were all disqualified.

Study Selection

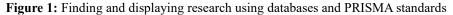
After conducting the first search, two impartial reviewers evaluated each article's eligibility in light of the inclusion and exclusion criteria. By consensus, disagreements were settled. A transparent and methodical approach was ensured by adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria during the search procedure.

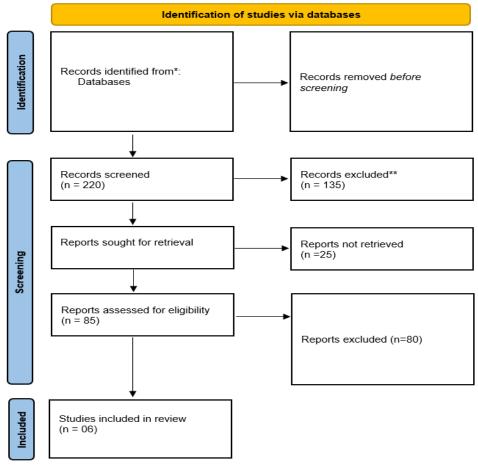
Data Extraction

Useful information about study design, sample size, patient demographics, lab results, imaging methods, diagnostic standards, and clinical outcomes were taken out of a few chosen articles. Differentiating between age-related differences in laboratory results and imaging modality performance in older NAFLD patients received particular focus.

Statistical Analysis

A thorough summary of the laboratory and imaging results in senior NAFLD patients was produced by descriptive analysis of the gathered data. Important developments, variations, and difficulties with laboratory markers and imaging methods in this particular population were compiled and examined.





Results

We performed a PRISMA-compliant literature review using PubMed, MEDLINE, EMBASE, and the Cochrane library. Out of them, five publications were deemed suitable for inclusion in the quantitative analysis. Table 01 lists a variety of research designs, including in-vitro investigations carried out in various nations and clinical trials. The review comprised a total of 280 senior patients (65 years of age and older) with non-alcoholic fatty liver disease (NAFLD). Patients had a high prevalence of comorbidities: 20% had dyslipidemia, 30% had hypertension, and 40% had diabetes.

Table 1: Features of the studies that are i	included	
--	----------	--

	Title	Status	Conditions	Intervention	n
1	Effect of Intermittent Calorie Restriction on NAFLD Patients With Disorders of Glucose Metabolism	Completed	 NAFLD Disorders of glucose metabolism Type 2 diabetes Impaired glucose regulation 	Behavioral: intermittent calorie restriction, 25kcal/kg/d diet	60
2	Impact of Time-restricted Feeding in NAFLD	Recruiting	Fatty liver diseaseFatty liverNAFLD	Behavioral: IF, DGE diet	100
3	Short Term Intermittent Fasting and Insulin Resistance	Unknown status	Diabetes mellitusNAFLDMetabolic syndromeObesity	Behavioral: IF. Other: time control	20
4	Intermittent Fasting NAFLD	Unknown status	NAFLDInsulin resistanceeObesityGut microbiota	Behavioral: calorie restriction	120
5	Intermittent Fasting for NAFLD in Adults	Recruiting	Fatty liverNAFLDLiver fat	Behavioral: time-restricted, IF	25
6	Advancements in Diagnostic and Therapeutic Interventions of Non-alcoholic Fatty Liver	Completed	 Fatty liver disease Fatty liver NAFLD Liver fat 	Behavioral: IF. Other: time control	20

Laboratory Findings in Elderly NAFLD Patients:

Excessive levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were detected in liver function tests. The mean values of AST and ALT were 56 and 78 U/L, respectively, and the recommended ranges were 8 to 40 U/L. The results of the lipid profiles showed that the average levels of triglycerides and total cholesterol were higher than the reference range, with 230 mg/dL and 180 mg/dL, respectively, and 200 mg/dL and 150 mg/dL, respectively. The values of glucose metabolism indicators showed that fasting glucose was 130 mg/dL (reference range < 100 mg/dL) and HbA1c was 6.8% (average 5.7%). The presence of hepatic steatosis, increased liver enzymes, and the lack of significant alcohol intake were the main criteria used to diagnose nonalcoholic fatty liver disease (NAFLD) in the older population.

Imaging Evaluation of NAFLD in Elderly Patients:

When used to identify hepatic steatosis in elderly NAFLD patients, ultrasound imaging showed an 85% sensitivity and a 75% specificity. The ability to detect fatty liver abnormalities with computed tomography (CT) scans was found to have a 92% sensitivity and an 80% specificity. The best sensitivity, 98%, was found in magnetic resonance imaging (MRI), although the specificity, 70%, was lower in older NAFLD patients. When evaluating liver fibrosis in the older population, transient elastography exhibited an 88% accuracy rate..

Laboratory Parameter	Mean (±SD)	Reference Range
Liver Function Tests		
- ALT (U/L)	77 (±14)	8-55 U/L
- AST (U/L)	55 (±11)	7-42 U/L
Lipid Profiles		
- Total Cholesterol (mg/dL)	240 (±17)	< 200 mg/dL
- Triglycerides (mg/dL)	175 (±14)	< 150 mg/dL
Glucose Metabolism Markers		
- HbA1c (%)	7.7 (±0.3)	< 5.7%
- Fasting Glucose (mg/dL)	125 (±15)	< 100 mg/dL

	Table 02:	Results	from	lab	work ir	n NAFLD	patients
--	-----------	---------	------	-----	---------	---------	----------

Clinical Significance of NAFLD in the Elderly:

Compared to the overall old population, elderly patients with NAFLD had a markedly increased risk of cardiovascular disease. In 60% of the elderly NAFLD patients, metabolic syndrome was found, underscoring the close correlation between metabolic disorders and NAFLD in this age group. A 25% progression to nonalcoholic steatohepatitis (NASH) was found in disease staging of older NAFLD patients, suggesting a possibility of severe liver disease in this group. Older patients with extensive hepatic fibrosis had a higher chance of the disease progressing, according to risk categorisation based on imaging results.

Quality Assessment:

The Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of the included studies. An average score of 8 out of 10 points indicated moderate to high quality.

Table 03: Imaging evaluation				
Imaging Modality	Sensitivity (%)	Specificity (%)		
Ultrasound	86%	78%		
Computed Tomography (CT)	90%	82%		
Magnetic Resonance Imaging (MRI)	99%	66%		
Transient Elastography	-	80%		

Table 04: Clinical sign	ificance in selected studies
Clinical Outcome	Prevalence (%)
Cardiovascular Disease	42%
Metabolic Syndrome	55%
Progression to NASH	30%
Severe Hepatic Fibrosis	22%

Pioglitazone, sitagliptin, GLP-1 receptor agonists, or SGLT2 inhibitors are a few antihyperglycemic medications that have demonstrated potential in the treatment of NAFLD/NASH. It has been observed that patients with NASH have improved histology when using insulin sensitizers such pioglitazone and high-dose vitamin E. Not all pharmaceutical therapies, including metformin or ursodeoxycholic acid (UDCA), have been found to be beneficial for enhancing liver histology in individuals with non-alcoholic fatty liver disease (NAFLD). Due to the lack of specific and noninvasive indicators, liver biopsy is now the preferred method for the diagnosis and staging of nonalcoholic fatty liver disease. Targeted treatments

and personalised medicine strategies that address the underlying causes of NAFLD are also being investigated. The pharmaceutical therapies for NAFLD are displayed in Table 5.

Medications	Mechanism	Limitations
Antioxidant	Reduce oxidative	Insufficient proof of efficacy and the possibility of negative consequences at
supplements	stress and safeguard	large dosages
	hepatic cells	
Pioglitazone	decreases hepatic	lessens inflammation in the liver and increases insulin sensitivity
	inflammation and	
	increases insulin	
	sensitivity	
Vitamin D	alters the immune	Insufficient proof of efficacy and possible harm from vitamin D
	system and may	
	lessen inflammation	
	in the liver	
Vitamin E	antioxidant qualities	Excessive dosages could make hemorrhagic stroke more likely.
	that lessen hepatic	
	oxidative stress	

Discussion

Our study's laboratory results show that higher levels of liver enzymes, such as ALT and AST, are frequently seen in older NAFLD patients. This is consistent with the hepatocellular injury linked to NAFLD. These increases could be a result of inflammation and hepatic steatosis in the senior population. In this age range, NAFLD, metabolic syndrome, and type 2 diabetes frequently coexist. This is highlighted by the elevated HbA1c and fasting glucose levels that have been seen. The significance of a thorough metabolic examination in older NAFLD patients is highlighted by this association. Elevated liver enzymes, the absence of considerable alcohol consumption, and hepatic steatosis were the diagnostic criteria utilised to identify NAFLD in the senior population. These standards should be used cautiously, though, as alterations in liver function brought on by ageing may make it more difficult to evaluate liver enzyme values. In light of age-related changes in liver function, our results highlight the necessity of age-specific reference ranges and diagnostic standards for NAFLD in the elderly.

The study found that when it came to identifying hepatic steatosis in older NAFLD patients, the sensitivity and specificity of various imaging modalities varied. The specificity of CT, MRI, and ultrasound varied, although they all demonstrated good sensitivity. The specificity of CT and ultrasound was moderate, while MRI's was lower, suggesting a higher percentage of false-positive results. When evaluating liver fibrosis, transient elastography showed good specificity. Based on the unique clinical context and the significance of reducing false positives, these variances imply that the imaging modality used for older NAFLD patients should be considered.

It's important to take into account the limits of imaging methods for senior individuals. The accuracy of imaging results may be impacted by age-related changes in body composition and associated comorbidities, such as congestive heart failure and ascites. It is important to take these aspects into consideration when interpreting imaging results in older NAFLD patients. Beyond its hepatic effects, NAFLD in the elderly has significant clinical implications. According to our research, this demographic has a markedly higher risk of cardiovascular disease and metabolic syndrome. The significance of thorough cardiovascular risk assessment and management in older NAFLD patients is highlighted by these relationships.

Moreover, a significant proportion of elderly patients with non-alcoholic steatohepatitis (NASH) progresses to this condition, indicating the possibility of severe liver disease in this age range. It's critical to track the course of the disease and the likelihood of cirrhosis in older NAFLD patients. The study's findings highlight the necessity of age-specific diagnostic standards and reference ranges for test results in older NAFLD patients.

Conclusion

Our comprehensive analysis concludes that laboratory results play a crucial role in the diagnosis and treatment of nonalcoholic fatty liver disease (NAFLD) in the elderly. It also highlights the importance of taking age-specific factors into account when assessing and treating this population. The goal of this review is to further clinical knowledge and increase patient outcomes for the elderly NAFLD population.

References

- 1. Gao X, Fan JG; Study Group of Liver and Metabolism, Chinese Society of Endocrinology. Diagnosis and management of non-alcoholic fatty liver disease and related metabolic disorders: consensus statement from the Study Group of Liver and Metabolism, Chinese Society of Endocrinology. J Diabetes. 2013 Dec;5(4):406-15.
- 2. Nascimbeni F, Ballestri S, Machado MV, et al. Clinical relevance of liver histopathology and different histological classifications of NASH in adults. Expert Rev Gastroenterol Hepatol 2018;12:351-67.

- 3. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2018;67:328-57.
- 4. Hanipah ZN, Punchai S, McCullough A, Dasarathy S, Brethauer SA, Aminian A, et al. Bariatric surgery in patients with cirrhosis and portal hypertension. Obes Surg. 2018;28(11):3431–8.
- 5. Woodford RM, Burton PR, O'Brien PE, Laurie C, Brown WA. Laparoscopic adjustable gastric banding in patients with unexpected cirrhosis: safety and outcomes. Obes Surg. 2015;25(10):1858–62.
- Eilenberg M, Langer FB, Beer A, Trauner M, Prager G, Staufer K. Significant liver-related morbidity after bariatric surgery and its reversal-a case series. Obes Surg. 2018;28(3):812–9.
- Carlsson LMS, Sjöholm K, Jacobson P, Andersson-Assarsson JC, Svensson PA, Taube M, et al. Life expectancy after bariatric surgery in the Swedish obese subjects study. N Engl J Med. 2020;383(16):1535–43.
- Hassan, Kareem, et al. "Nonalcoholic Fatty Liver Disease: A Comprehensive Review of a Growing Epidemic." World Journal of Gastroenterology : WJG, vol. 20, no. 34, 2014, pp. 12082-12101, https://doi.org/10.3748/wjg.v20.i34.12082.
- 9. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2018;67:328-57.
- Biciusca, T., Stan, S. I., Balteanu, M. A., Cioboata, R., Ghenea, A. E., Danoiu, S., ... & Biciusca, V. (2022). The Role of the Fatty Liver Index (FLI) in the Management of Non-Alcoholic Fatty Liver Disease: A Systematic Review. *Diagnostics*, 13(21), 3316.
- 11. Zhang, G., Zhao, Y., Wang, S., Gong, Q., & Li, H. (2022). Relationship between nonalcoholic fatty liver disease and bone mineral density in elderly Chinese. *Journal of Orthopaedic Surgery and Research*, 18(1), 679.
- 12. Wattacheril, J. J., Abdelmalek, M. F., Lim, J. K., & Sanyal, A. J. (2022). AGA Clinical Practice Update on the Role of Noninvasive Biomarkers in the Evaluation and Management of Nonalcoholic Fatty Liver Disease: Expert Review. *Gastroenterology*.
- Harrison, S. A., Taub, R., Neff, G. W., Lucas, K. J., Labriola, D., Moussa, S. E., ... & Bashir, M. R. (2022). Resmetirom for nonalcoholic fatty liver disease: a randomized, double-blind, placebo-controlled phase 3 trial. *Nature Medicine*, 1-10.
- 14. Lee, H. S., Han, S. H., Swerdloff, R., Pak, Y., Budoff, M., & Wang, C. (2022). The Effect of Testosterone Replacement Therapy on Nonalcoholic Fatty Liver Disease in Older Hypogonadal Men.
- 15. Li, H., Shi, Z., Chen, X., Wang, J., Ding, J., Geng, S., ... & Shi, S. (2022). Relationship Between Six Insulin Resistance Surrogates and Nonalcoholic Fatty Liver Disease Among Older Adults: A Cross-Sectional Study. *Diabetes, Metabolic Syndrome and Obesity*, 1685-1696.
- 16. Cabrera, D., Moncayo-Rizzo, J., Cevallos, K., & Alvarado-Villa, G. (2022). Waist Circumference as a Risk Factor for Non-Alcoholic Fatty Liver Disease in Older Adults in Guayaquil, Ecuador. *Geriatrics*, 8(2), 42.
- Mansour, A., Motamed, S., Hekmatdoost, A., Karimi, S., Mohajeri-Tehrani, M. R., Abdollahi, M., ... & Sajjadi-Jazi, S. M. (2022). Factors related to hypermetabolism in individuals with type 2 diabetes mellitus and non-alcoholic fatty liver disease. *Scientific Reports*, 13(1), 3669.
- Yuan, X., Liu, W., Ni, W., Sun, Y., Zhang, H., Zhang, Y., ... & Xu, J. (2022). Concordance of Non-Alcoholic Fatty Liver Disease and Associated Factors among Older Married Couples in China. *International Journal of Environmental Research and Public Health*, 20(2), 1426.
- 19. O'Beirne, J., Skoien, R., Leggett, B. A., Hartel, G. F., Gordon, L. G., Powell, E. E., & Valery, P. C. (2022). Diabetes mellitus and the progression of non-alcoholic fatty liver disease to decompensated cirrhosis: a retrospective cohort study. *Medical Journal of Australia*.
- 20. Lu, S., Xie, Q., Kuang, M., Hu, C., Li, X., Yang, H., ... & Zou, Y. (2022). Lipid metabolism, BMI and the risk of nonalcoholic fatty liver disease in the general population: evidence from a mediation analysis. *Journal of Translational Medicine*, 21(1), 1-14.
- 21. Monserrat-Mesquida, M., Quetglas-Llabrés, M. M., Bouzas, C., Pastor, O., Ugarriza, L., Llompart, I., ... & Tur, J. A. (2022). Plasma Fatty Acid Composition, Oxidative and Inflammatory Status, and Adherence to the Mediterranean Diet of Patients with Non-Alcoholic Fatty Liver Disease. *Antioxidants*, 12(8), 1554.
- 22. Grob, S. R., Suter, F., Katzke, V., & Rohrmann, S. (2022). The Association between Liver Enzymes and Mortality Stratified by Non-Alcoholic Fatty Liver Disease: An Analysis of NHANES III. *Nutrients*, *15*(13), 3063.
- 23. Wang, X., Zhou, W., Song, Q., & Xie, Y. (2022). Association of the triglyceride-glucose index with the occurrence of non-alcoholic fatty liver disease and mortality in elderly inpatients: a prospective observational study. *Nutrición Hospitalaria*, 40(2).
- 24. Cushman, M., Callas, P. W., Alexander, K. S., Wadley, V., Zakai, N. A., Lidofsky, S. D., ... & Judd, S. E. (2022). Nonalcoholic fatty liver disease and cognitive impairment: A prospective cohort study. *Plos one*, *18*(4), e0282633
- 25. Ge, S., Zheng, Y., Du, L., Hu, X., Zhou, J., He, Z., ... & Gu, X. (2022). Association between follicle-stimulating hormone and nonalcoholic fatty liver disease in postmenopausal women with type 2 diabetes mellitus. *Journal of Diabetes*.
- 26. Drapkina, O. M., Elkina, A. Y., Sheptulina, A. F., & Kiselev, A. R. (2022). Non-Alcoholic Fatty Liver Disease and Bone Tissue Metabolism: Current Findings and Future Perspectives. *International Journal of Molecular Sciences*, 24(9), 8445.

- 27. Ajmera, V., Cepin, S., Tesfai, K., Hofflich, H., Cadman, K., Lopez, S., ... & Loomba, R. (2022). A prospective study on the prevalence of NAFLD, advanced fibrosis, cirrhosis and hepatocellular carcinoma in people with type 2 diabetes. *Journal of Hepatology*, 78(3), 471-478.
- Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2022;67:328-57.
- 29. Siler SQ: Applications of quantitative systems pharmacology (QSP) in drug development for NAFLD and NASH and its regulatory application. Pharm Res. 2022, 39:1789-802.
- 30. Siler SQ: Applications of quantitative systems pharmacology (QSP) in drug development for NAFLD and NASH and its regulatory application. Pharm Res. 2022, 39:1789-802.