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METABOLIC ASSOCIATED FATTY LIVER DISEASE (NON-ALCOHOLIC FATTY LIVER DISEASE) AMONG PATIENTS WITH TYPE 2 DIABETES IN SAUDI ARABIA: SYSTEMATIC REVIEW AND META ANALYSIS

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Abstract:

Background: Non-alcoholic fatty liver disease (NAFLD) is common among patients with type 2 diabetes. However, it is often ignored. When co-exist they exacerbate each other serious consequences. No meta-analysis has assessed NAFLD among patients with diabetes in Saudi Arabia. We aimed to investigate the prevalence and predictors of non-alcoholic fatty liver disease among patients with type 2 diabetes in Saudi Arabia.

Methods: three databases were searched (PubMed, MEDLINE, Cochrane Library, and Web of Science for articles published in English from the first published article up to March 2023. The following terms were used: type 2 diabetes, non-alcoholic fatty liver disease, metabolic associated fatty liver disease, predictors, alanine aminotransferase (ALT), aspartate aminotransferase (AST), Saudi Arabia, and using the protean "AND"and "OR".

Results: There were 1139 patients from three cross-sectional studies, ALT was higher among patients with NAFLD, odd ratio, 3.30, 95% CI, 3.12-3.49, P-value <0.001, and the Chi-square was1.07. No differences were evident between patients with and without NAFLD regarding AST, odd ratio, -0.00, 95% CI, -5.86-5.86, P-value, 1.0, and the Chi-square was18.03, and HDL, odd ratio, -0.53, 95% CI, -1.21-0.15, P-value, 0.12, and the Chi-square was77.28. NAFLD prevalence was (40% to 80.8.Conclusion: Non-alcoholic fatty liver disease was prevalent among patients with type 2 diabetes in Saudi Arabia and is associated with high ALT, while, high-density lipoproteins and AST were not. Healthcare and treating physicians might need to screen patients with type 2 diabetes for NAFLD. Further larger studies assessing the bone mineral density at different sites are needed.

Keywords: type 2 diabetes, non-alcoholic fatty liver disease, Saudi Arabia.

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1. INTRODUCTION:

Diabetes mellitus and non-alcoholic fatty liver disease (NAFLD) are two common chronic diseases that cause a significant burden of morbidity and mortality worldwide. Globally, approximately 10.5% of the population has diabetes, with the Kingdom of Saudi Arabia being among the countries with the highest prevalence of the disease (Sun et al., 2022; Mirghani et al., 2017). NAFLD, a chronic liver disease, has also reached epidemic proportions worldwide, with prevalence ranging from 20% to 30% in the general population (Lee, 2014; Yu et al., 2013).

Non-alcoholic fatty liver disease (NAFLD) is a multi-system disease that affects nearly one-quarter of the global population (Targher et al., 2020). NAFLD is the most common cause of chronic liver disease and non-alcoholic steatohepatitis (NASH), a more severe form of NAFLD, is projected to become the leading cause of liver transplantation (Targher et al., 2020). Beyond its impact on the liver, NAFLD is a serious disease with serious complications, including liver cirrhosis and hepatocellular carcinoma (HCC).

The prevalence of NAFLD in patients with diabetes reported in previous studies ranges from 50% to 87%, and a meta-analysis found that 55.5% of patients with diabetes had NAFLD, with more than one-third progressing to steatohepatitis and approximately 17% developing advanced fibrosis (Lazarus et al., 2022; Al Humayed et al., 2020; Younossi et al., 2019). Despite the potentially fatal consequences of NAFLD, it is often overlooked, especially in the Kingdom of Saudi Arabia, where the situation is particularly concerning, with a projected increase in NAFLD prevalence of 87%, a 187% increasing fibrosis and hepatocellular carcinoma, and 204,000 liver-related death by the year 2030 (Sanai et al., 2021).

A registry-based analysis conducted in Saudi Arabia found that patients with NAFLD had high rates of dyslipidemia (41.7%), diabetes (35.3%), and hypertension (28.4%). Interestingly, these comorbidities were more common in patients with normal levels of alanine aminotransferase (ALT) than in patients with elevated levels (Alswat et al., 2021). The impact of antidiabetic medications on NAFLD is a matter of debate, with some studies demonstrating improvement and others finding no benefit (Kumar et al., 2021; Zafar et al., 2022).

On the other hand, patients with NAFLD (both children and adults) had a high rate of osteoporosis, the released cytokines from the liver, vitamin D, and sedentary life are to blame (Yilmaz et al., 2012).

Thus, the current review aimed to assess non-alcoholic fatty liver disease among patients with diabetes mellitus in Saudi Arabia.

2. Methods:

Eligibility criteria according to PICOS:

A systematic literature search was conducted in four databases; Web of Science, PubMed, SCOPUS, and Cochrane library for relevant articles published in the English language and investigated the prevalence of the metabolic-related fatty liver disease among diabetic patients in Saudi Arabia. The studies from inception up to March 2023 were eligible.

Inclusion criteria:

Studies were eligible if they assessed non-alcoholic fatty liver disease among patients with type 2 diabetes in Saudi Arabia. Prospective, retrospective, cross-sectional, and case-control studies were included.

Exclusion criteria:

Case reports, case series, and animal studies were not included. Abstracts, opinions, letters, editorials, and expert opinions were also excluded.

Outcome measures:

The outcome measure is the prevalence and predictors of non-alcoholic fatty liver disease among patients with type 2 diabetes. The diagnosis of NAFLD was based on ultrasonography.

The literature search:

We searched PubMed, MEDLINE, Cochrane Library, SCOPUS, and Web of Science for articles published in English from the first inception up to February 2023. Two researchers (W. B. and H. M) screened the titles, abstracts, and references of the included studies for relevant articles. Any discrepancy was solved by agreement. The term used were: non-alcoholic fatty liver disease, metabolic associated fatty liver disease, Saudi Arabia, and type 2 diabetes in different combinations using the protean "AND" and "OR".

DATA ANALYSIS:

The most recent RevMan was used. The continuous data were entered manually to test the relationship between NAFL, ALT, AST, and HDL; the fixed or random effects were used depending on the level of heterogeneity. A P-value for the Chi-Square and heterogeneity at <0.05 was considered significant.

Figure 1. Nonalcoholic fatty liver disease and diabetes mellitus, Saudi Arabia

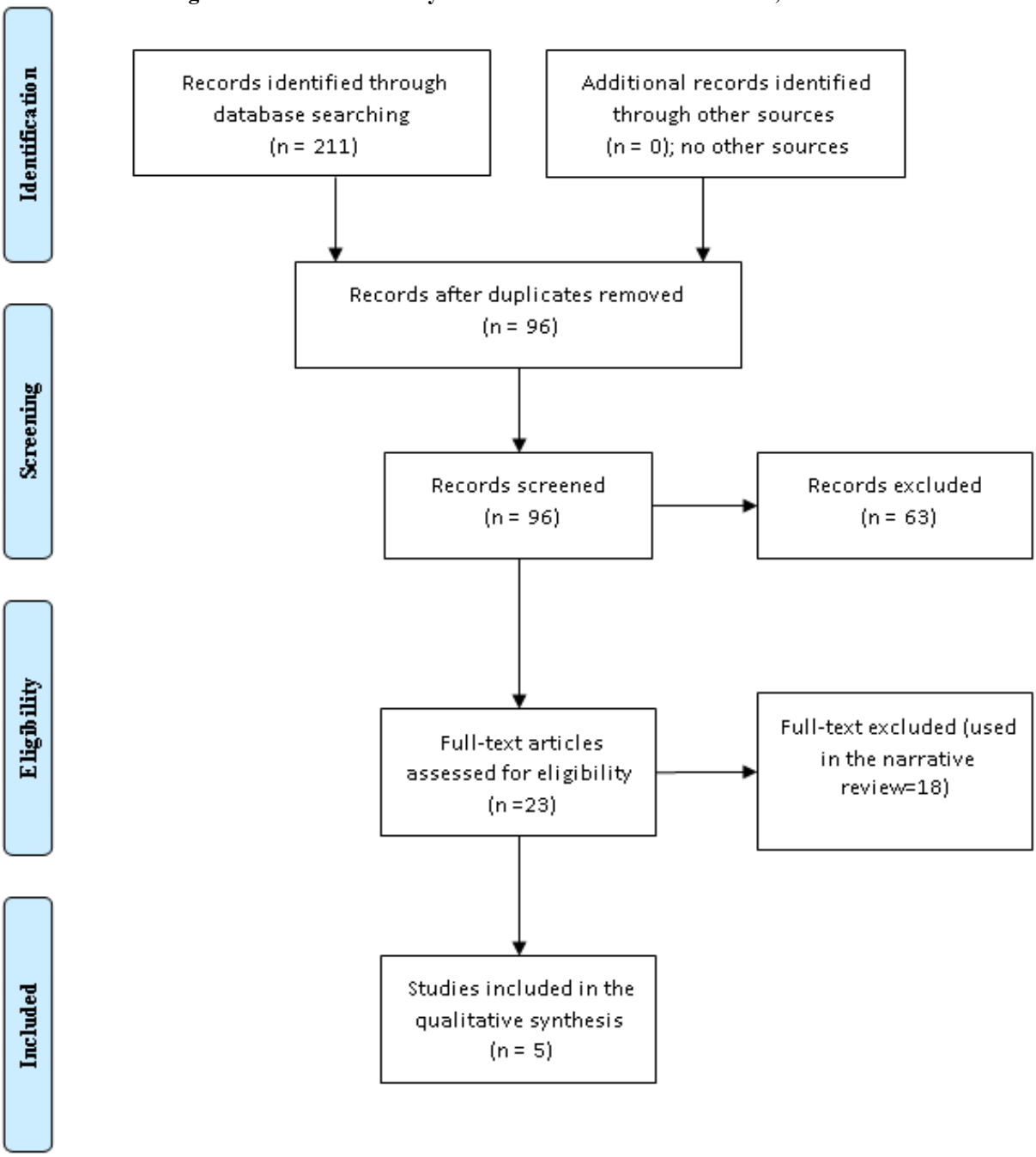


Table 1. Non-alcoholic fatty liver disease among patients with diabetes, Saudi Arabia.

Author	Study type	NAFLD Prevalence	Region	HbA1c	ALT status	AST status
Alamri et al. 2021 [12]	Retrospective , 100 patients	40%	Taif, West	Not mentioned	Raised 17%	Raised in 34%
Alsabaani et al. 2021 [13]	Retrospective , 245 patients	72.8%	Abha, Southwest	8.7	Raised in 10.6%	Raised in 24.9%
Alfadda et al. 2022 [14]	Crosssectional, 490	80.8%	Riyadh, Central	8.3%±1.9	26.5±18.5	21.9±13.7
Al Humayed et al. 2020 [15]	Crosssectional, 237	73.4%	Abha, Southwest	8.7	25.8	20.2
Ajabnoor et al. 2023 [16]	Crosssectional, 67	41.8%	Jeddah, West	8.7 ± 2.1	19.45±11.89	18.57±8.1

Table 2. Non-alcoholic fatty liver disease among patients with diabetes, Saudi Arabia.

Author	Age/years	Females/ males	Obesity and overweight % BMI (mean± SD)	Duration of diabetes	NAFLD association
Alamri et al. 2021 [12]	26-111	53/47	Not mentioned	Not mentioned	Associated with age, high fasting glucose, and low platelets.
Alsabaani et al. 2021 [13]	57.1 ±13.5	61/117	76%	10.1 ± 8.3	Associated with BMI, raised ALT, and HDL
Alfadda et al. 2022 [14]	49.9±7.5	228/262	69.7%	11.46	Associated with BMI, waist circumference, raised ALT, and HDL
Al Humayed et al. 2020 [15]	56.5	80/175	29.9	10.7	Associated with ALT
Ajabnoor et al. 2023 [16]	52±11.25	45/22	94.9%	More than ten years in 58.4%	Associated with diastolic blood pressure and HDL

3. RESULTS:

Characteristics of the included studies:

There were five cross-sectional studies, two were conducted in the West, two were published in the Southwest, and one from Central Region, the studies included patients. The glycated hemoglobin ranged from 8.3 to 8.7, ALT ranged from19.45±11.89 to 26.5±18.5 and raised from 10.6% to 17%, and AST ranged from18.57±8.1 to 21.9±13.7 and raised in 24.9% to 34%. Table 1.

In the present study, the age of the patients ranged from 26 to 111 years, 69.7% to 94.9% were obese; the duration of diabetes was 11.46 to 10.1 ± 8.3 years.

Prevalence and predictors of non-alcoholic fatty liver disease:

In the present meta-analysis, four studies assessed NAFLD and included 1139 participants. Non-alcoholic fatty liver disease ranged from 40% in the West (Alamri et al., 2021) to 80.8% in Central Region (Alfadda et al., 2022). High-density lipoproteins and ALT was a predictor of NAFLD, while AST and HDL were not. Table 2 and figures 2-4.

In the present meta-analysis, ALT was higher among patients with NAFLD, odd ratio, 3.30, 95% CI, 3.12-3.49, P-value <0.001, and the Chi-square was1.07. No heterogeneity was found, I^2=0.0%, and the P-value for heterogeneity, was 0.59. Figure 2.

No differences were evident between patients with and without NAFLD regarding AST, odd ratio, -0.00, 95% CI, -5.86-5.86, P-value, 1.0, and the Chi-square was 18.03. Significant heterogeneity was found, I^2=89%, and the P-value for heterogeneity, 0.0001, and HDL, odd ratio, -0.53, 95% CI, -1.21-0.15, P-value, 0.12, and the Chisquare was77.28. Significant heterogeneity was found, I^2=97%, and the P-value for heterogeneity, 0.00001. Figures 3 &4.

Figure 2. A comparison of ALT levels among patients with diabetes with and without NAFLD.

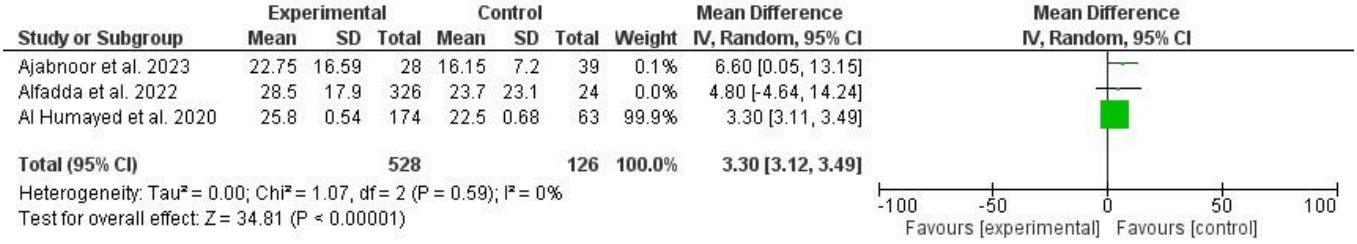


Figure 3. A comparison of AST levels among patients with diabetes with and without NAFLD.

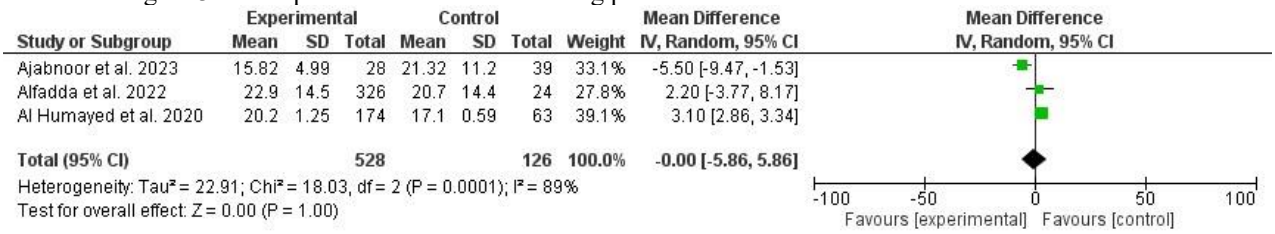
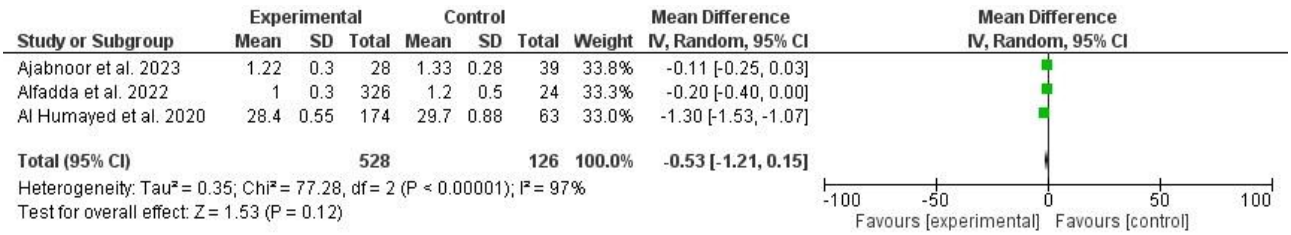


Figure 4. A comparison of HDL levels among patients with diabetes with and without NAFLD.



4. DISCUSSION:

Obesity and diabetes are on the rise in Saudi Arabia, as evidenced by the recent study by Mohamed et al. (2022), which found that one-third of the population will have diabetes by the age of 40. This will have a profound impact on the health of the Saudi population, both in terms of the direct costs of treating these conditions and the indirect costs associated with lost productivity and disability.

A number of studies have found that the prevalence of NAFLD is high among people with diabetes in Saudi Arabia, ranging from 40% to 80.8%. In particular, studies by Alfadda et al. (2022), Alsabaani et al. (2021), and AlHumaid, et al. (2020) found high rates of NAFLD in people with diabetes, highlighting the need for effective intervention and management strategies to address this issue.

Interestingly, the high rates of NAFLD found in Saudi Arabia are similar to those observed in another Gulf country, the United Arab Emirates, where a study by Labenz et al. (2022) found a prevalence of 68.1%. In contrast, a study conducted in Germany by Targher et al. (2020) found a much lower prevalence of 7.8%. These findings suggest that NAFLD may be more common in Gulf countries than in other parts of the world, possibly due to differences in dietary habits and lifestyle.

A systematic review and meta-analysis by Soni et al. (2019) found that the prevalence of NAFLD varied by geographical region, with higher rates in the Middle East and South America and lower rates in Africa. The authors suggested that this variation may be due to differences in genetics, diet, and lifestyle between regions. For example, the Middle East and South America have high rates of obesity, while Africa has a lower prevalence. These differences may also be related to socioeconomic factors and access to healthcare.

In the general population, the prevalence of NAFLD has been estimated at 25.24% (Younossi et al., 2016). Moreover, research has shown that diabetes is associated with a more than two-fold increased risk of developing NAFLD (Jarvis et al., 2020). The high rates of both NAFLD and diabetes, and the link between the two conditions, highlights the importance of addressing these two conditions in an integrated manner. This may involve interventions that target both conditions simultaneously, such as lifestyle changes and pharmacological treatments.

A meta-analysis by Younossi et al. (2019) also reported a high prevalence of NAFLD among patients with diabetes (55.5%), consistent with the results of the current study. However, it is important to note that the included studies in both meta-analyses were conducted in different regions of the world and may have included different patient populations. Therefore, the results should be interpreted with caution and further studies are needed to confirm these findings.

The presence of both NAFLD and diabetes has been shown to increase the risk of developing serious complications, including chronic liver disease, hospitalization, hepatocellular carcinoma, and death (Targher et al., 2007). Furthermore, the combination of NAFLD and diabetes can exacerbate the risk of atherosclerosis through dyslipidemia, hypertension, and poor glycemic control (Bril et al., 2020). This highlights the importance of early diagnosis and intervention for patients with both conditions to minimize the risk of developing these serious complications.

This meta-analysis found that alanine aminotransferase (ALT) levels, but not aspartate aminotransferase (AST) levels, were associated with NAFLD, in line with previous research (Mandal et al., 2018). The meta-analysis also found an association between NAFLD and low high-density lipoprotein (HDL) levels, in agreement with Krishan and colleagues' review of the literature, which found that the dyslipidemia associated with NAFLD and diabetes is atherogenic (Krishan et al., 2017).

The findings from this meta-analysis, and the available literature, suggest that NAFLD is linked to cardiovascular disease, mortality, decreased pulmonary function, and chronic renal failure (Mantovani et al., 2021, 2019, 2019).

Given the potentially serious consequences of NAFLD, it is important to screen for the disease to prevent its progression and associated complications. However, international guidelines on the screening of NAFLD are not uniform, with the European guidelines [21,22] recommending screening for the disease, while the UK National Institute for Care Excellence (NICE) and the American Association for the Study of Liver Diseases (AASLD) are not recommend as a screening for NAFLD, as there is uncertainty about how to interpret the results, the cost-effectiveness of screening, and the role of pharmacological interventions [23,24].

5. CONCLUSION:

Nonalcoholic fatty liver was prevalent among patients with type 2 diabetes in Saudi Arabia. Increasing awareness about NAFLD among patients with type 2 diabetes is recommended. Healthcare and treating physicians might need to screen patients with type 2 diabetes for NAFLD for better selection of the optimal antidiabetic medication. Further larger studies assessing the synergistic effects of diabetes and non-alcoholic fatty liver are needed.

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Ethical approval: not applicable

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Conflict of interest: The authors declare that there is no conflict of interest.

Data and materials availability: All data sets collected during this study are available upon reasonable request from the corresponding author

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