https://doi.org/10.29309/TPMJ/2024.31.12.8405

The Professional Medical Journal
www.theprofesional.com
2024, Volume, 31 Issue, 12

ORIGINAL ARTICLE

Efficacy of Vitamin E Versus Pioglitazone in Treating Non-Alcoholic Fatty Liver Disease (NAFLD) without Diabetes.

Muhammad Owais Fazal[1], Ghulam Abbas Tahir[2], Yasir Yaqoob[3], Ahmad Zeeshan[4], Rabia Sharif[5], Muhammad Usman Musharraf[6]

Article Citation: Fazal MO, Tahir GA, Yaqoob Y, Zeeshan A, Sharif R, Musharraf MU. Efficacy of Vitamin E Versus Pioglitazone in Treating Non-Alcoholic Fatty Liver Disease (NAFLD) without Diabetes. Professional Med J 2024; 31(12):1685-1689. https://doi.org/10.29309/TPMJ/2024.31.12.8405

ABSTRACT… Objective: To compare the effectiveness of vitamin E in comparison with Pioglitazone in the management of NAFLD without Diabetes. **Study Design:** Randomized Control Trial. **Setting:** Outpatient Department of Allied Hospital, Faisalabad. **Period:** Dec 2023 to May 2024. **Methods:** The Ethics Review Committee of Faisalabad Medical University was taken on board and patients having the characteristics of the set Inclusion Criteria were enrolled as allowed. Selected individuals were counseled regarding the study and their consent was sought. Using a computer-generated random number table, two main groups were formed out of the participants, Group A and Group B. Group A was given 800IU of Vitamin E daily. Group B received Pioglitazone 30mg daily. Patients were monitored for efficacy over three months by tracking ALT levels as specified in the operational definition. Follow-up was ensured through contact numbers. **Results:** In our study of 722 cases (361 in each group), the mean age was 41.25±6.41 years in Group A and 41.23±6.56 years in Group B. Males comprised 60.11% (n=217) of Group A and 59.56% (n=215) of the Group B, while females accounted for 39.89% (n=144) out of Group A and 40.44% (n=146) of the Group B. Efficacy comparison showed that 49.72% (n=147) in Group A and 31.30% (n=113) in Group B achieved efficacy, with a p-value of 0.008, pointing out a considerable difference. **Conclusion:** Our study succeeded in establishing the better efficacy of Vitamin E in treating NAFLD compared to Pioglitazone.

Key words: Efficacy, Non-alcoholic Fatty Liver Disease, Non-diabetics, Pioglitazone, Vitamin E.

INTRODUCTION

NAFLD is an amalgam of a variety of different conditions, which include, steatosis, steatohepatitis, and cirrhosis, occurring without excessive alcohol consumption.[1] Hepatic fibrosis is present in 40% of the cases with cirrhosis developing in 9-25% of the patients, leading to decompensated liver disease in 30-50% of cirrhotic individuals. This condition is increasingly acknowledged as a significant public health concern, particularly in the United States, and its prevalence is on the rise in the Asia-Pacific area and, South Asia. However, the data from Pakistani communities is still not enough.[3,4]

Some of the factors that have been established in association with NAFLD are Diabetes, specifically Type II, increased insulin resistance, a high BMI, and Dyslipidemias.[5] Moreover, insulin resistance and oxygen free radicals are also postulated as an underlying mechanism of liver injury, making them prime targets of studies pertinent to treatment modalities.[6] Various treatment modalities are proposed for non-alcoholic fatty liver disease, including weight reduction, metformin, thiazolidinediones, statins, pentoxifylline, and vitamin E. Randomized controlled trials have consistently shown positive outcomes with vitamin E and the thiazolidinedione i.e. Pioglitazone.[7] Notably, Vitamin E shows promising improvements (43% vs. 19%, p=0.001) when comparing it with a placebo, and insignificant results with Pioglitazone (34% vs. 19%, p=0.04).[8]

Despite the evidence, vitamin E is not widely utilized in clinical practice for NAFLD treatment and is often overlooked. The aim is to compare and establish the better one out of vitamin E and

1. MBBS, MCPS (Med), FCPS (Med) MRCP (Glasg UK), PG DIP (Diabetes), CHPE, MBA (IRE), MSPH, Associate Professor, FMU.
2. MBBS, FCPS (Med), CHPE, Assistant Professor Medicine, AHF.
3. MBBS, FCPS (Med), Assistant Professor, AHF.
4. MBBS, FCPS (Med), Assistant Professor, AHF.
5. MBS, FCPS (Gyn/Obs), Senior Registrar, AHF.
6. MBBS, FCPS (Med), FCPS (Endo), Senior Registrar Medicine, AHF.

Correspondence Address:
Dr. Ghulam Abbas Tahir
Department of Medicine
AHF.
drabbas_936@hotmail.com

Article received on: 14/08/2024
Accepted for publication: 16/10/2024

Pioglitazone in treating NAFLD, aiming to provide insights into its clinical utilization in patients without diabetes.

OPERATIONAL DEFINITION

NAFLD

NAFLD in a patient was labeled only after ultrasonographic (radiological) evidence was supported by raised ALT in selected subjects.

Efficacy

- Efficacy was measured by monitoring ALT/ Ultrasound at three months. The drug was considered effective if ALT became normal (7 to 56 IU/L) at three months of therapy.

Hypothesis

- Vitamin E is superior to Pioglitazone in NAFLD treatment in the non-diabetic population

METHODS

This randomized controlled trial was conducted in the outpatient department (OPD) of Medicine at Allied Hospital, Faisalabad, over a period of six months Dec 2023 to May 2024 after approval from the ethical review committee vide letter No. 48-ERC/FMU/2022/23/354 Dated 27-11-2023. The sample size was determined using the WHO calculator for two proportions, resulting in 722 participants, with 321 in each group. The study maintained a 5% level of significance and an 80% power. The proportions for comparison were P1 = 43% and P2 = 34%. A nonprobability consecutive sampling technique was used to select participants. Inclusion criteria included men and women aged 18-50 years diagnosed with non-alcoholic fatty liver disease (NAFLD) as defined operationally. Exclusion criteria consisted of individuals with fasting blood sugar levels exceeding 126 mg/dL or postprandial blood sugar over 200 mg/dL, those consuming alcohol above 20g/day for females and 30g/ day for males, individuals positive for hepatitis B or C on serology, and patients receiving medications known to cause steatohepatitis (such as chemotherapy drugs, glucocorticoids, methotrexate, and others). Additional exclusion criteria included patients with New York Heart Association (NYHA) class 2 to 4 disease and those taking statins.

Data Collection

Following acceptance from the Institute's ERC individuals fulfilling inclusion criteria were recruited. All enrolled patients signed consent for the study. Random allocation of participants into Groups A and B was done. 800IU per day of Vitamin E to Group A and 30mg per day of Pioglitazone to Group B was dispensed. Patients were monitored for efficacy over three months by assessing ALT levels and ultrasonographic improvements, as outlined in the operational definition. Follow-up was ensured through the collection of contact information from participants.

Data Analysis

SPSS Version 20 is used for data handling and interpretation. Quantitative variables, including age and ALT levels, were subjected to the calculation of Mean and SD, in contrast, frequency, and percentage for gender and efficacy as they are qualitative variables. A chi-squared test (significance level of $p \leq 0.05$) helped the comparison among the two groups. Confounding variables, including baseline ALT levels, age, and gender, were managed through stratification. A post-stratification Chi-squared test was done to strengthen the results (significance level of $p \leq 0.05$).

RESULTS

A total of 722 patients (361 in either group) matching the inclusion factors were gathered for assessment of the superiority of Vitamin E in NAFLD in the general population (non-diabetics). 17.45% (n=63) of Group A and 17.73% (n=64) of Group B lie between the 18-35 years age slot. 82.55% (n=298) of Group A and 82.27% of Group B were between 36-50 year age window (mean +SD 41.25+6.41 years in Group A and 41.23+6.56 years in Group B. 60.11% (n=217) males in Group A, 59.56% (n=215) in Group B, whereas 39.89% (n=144) females in Group A and 40.44%(n=146) in Group B. Baseline ALT comparison shows Group A had 88.00+5.13 (IU/L) whereas 87.96+4.96(IU/L) in Group B. (Table-I)

Vitamin E vs. pioglitazone in terms of treatment shows that 49.72% (n=147) in Group A and 31.30% (n=113) in Group B had better efficacy, whereas 59.28% (n=214) in Group A and 68.70% (n=248) in Group B had no efficacy, significant p-value of 0.008. (Table-II)

Confounding factors (Baseline ALT, age, and gender) were sought and controlled with stratification. Post-stratification chi-square test applied with p= <0.05 as significant. Other effect modifiers were controlled through stratification. (Table-III to V)

Indicator	Group A (n= 361)		Group B (n=361)	
Age (in years)	**No. of Patients**	**%**	**No of Patients**	**%**
18-35	63	17.45	64	17.73
36-50	298	82.55	297	82.27
Total	361	100	361	100
Mean+SD	**41.25+ 6.41**		**41.23 + 6.56**	
Gender				
Male	217	60.11	215	59.56
Female	144	39.89	146	40.44
Total	361	100	361	100
ALT(IU/L)	**Mean**	**SD**	**Mean**	**SD**
..	88.00	5.13	87.96	4.96

Table-I. (n=722)

Efficacy	Group-A (n=361)		Group-B (n=361)	
	No. of Patients	**%**	**No. of Patients**	**%**
Yes	147	40.72	113	31.30
No	214	59.28	248	68.70
Total	361	100	361	100

Table-II. Comparative Efficacy of Pioglitazone vs. Vitamin E in Treating NAFLD without diabetes (n=722, P-value=0.008)

AGE: 18-30 years

Group	Efficacy		P-Value
	Yes	**No**	
A	23	40	0.63
B	26	38	

AGE: 31-50 years

Group	Efficacy		P-Value
	Yes	**No**	
A	124	174	0.26
B	87	149	

Table-III. Efficacy of Pioglitazone and Vitamin E in Treating NAFLD in Non-Diabetic Patients: Age-Based Stratification (n=722)

Gender: Male

Group	Efficacy		P-Value
	Yes	**No**	
A	79	59	0.002
B	61	93	

Gender: Female

Group	Efficacy		P-Value
	Yes	**No**	
A	68	87	0.07
B	52	42	

Table-IV. Efficacy of Pioglitazone and Vitamin E in Treating NAFLD in Non-Diabetic Patients: Gender-Based Stratification (n=722)

ALT: 80-90 IU/L

Group	Efficacy		P-Value
	Yes	**No**	
A	85	121	0.04
B	66	143	

ALT: >90 IU/L

Group	Efficacy		P-Value
	Yes	**No**	
A	62	93	0.09
B	47	105	

Table-V. Effectiveness of Pioglitazone and Vitamin E for Treating NAFLD in Non-Diabetic Patients: Baseline ALT Stratification" (n=722)

DISCUSSION

NAFLD means excess fat in the liver, namely triglycerides[10], in the absence of secondary factors like alcoholism, steatogenic medications, or genetics.[11,12] NAFLD is linked with many adverse hepatic outcomes like accelerated hepatic fibrosis (41%), cirrhosis(20-25%), advanced liver failure (5.4%), and heart diseases (CVD).[13] There is no consensus on the exact mechanism that underlies the disease process[14,15], leading to empirical therapy primarily focusing on treating associated conditions such as diabetes, excessive weight gain, and hyperlipidemia through lifestyle improvements like reducing weight, dietary adjustments, and physical activity. Non-pharmacological and pharmacological interventions have been explored, yet determining the most productive approach for managing NAFLD remains uncertain.[14]

Vitamin E is underutilized for NAFLD treatment despite its potential efficacy in clinical practice.[17,18] We intend to assess the potential of vitamin E in treating NAFLD to reform clinical recommendations for its usage in patients without diabetes.

In the review of our study, out of 722 cases (361 in each group), Group A received 800 IU of Vitamin E daily, while Group B took 30 mg per day of Pioglitazone. The mean age was 41.25±6.41 years, and 41.23±6.56 years in Groups A and B respectively. In the context of gender segregation, 60.11% (n=217) were males and 59.56% (n=215) in Group B, while 39.89% (n=144) of Group A and 40.44% (n=146) of Group B were females. At a glance, the study exhibited a significant difference in vitamin E efficacy with evidence of 49.72% (n=147) in Group A and 31.30% (n=113) in Group B having better outcomes, the p-value being 0.008.

Comparing our results with the literature, vitamin E therapy demonstrated a higher impact on disease progression than placebo (43% vs. 19%, p=0.001). However, similar results for Pioglitazone and placebo (34% vs. 19%, p=0.04). Previous studies did not directly compare Pioglitazone and vitamin E in treating NAFLD.

Experimental models evaluating the effects of vitamin E in treating NAFLD have shown promising results, including attenuation of steatohepatitis, reduction in oxidative stress markers, and improvement in histological parameters.[18-20] Additionally, vitamin E has been associated with reductions in dyslipidemia, hepatic lipid accumulation, and hepatocellular ballooning in NAFLD/NASH patients.

In conclusion, our study supports the hypothesis that vitamin E may be more effective than Pioglitazone as a therapy for NAFLD without Diabetes. The horizon for more research to support our findings is still vast. There remains room for research validating better treatment modalities and novel introductions.

CONCLUSION

Our findings suggest that Vitamin E exhibits greater efficacy than Pioglitazone in treating NAFLD in non-diabetic patients.

STUDY LIMITATIONS

Nevertheless, the lack of local data addressing this issue necessitates further research across various health centers to validate our findings.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SOURCE OF FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

REFERENCES

1. Maurice J, Manousou P. **Non-alcoholic fatty liver disease.** Clinical Medicine. 2018; 18(3):245-50.

2. Heyens LJM, Busschots D, Koek GH, Robaeys G, Francque S. **Liver fibrosis in non-alcoholic fatty liver disease: From liver biopsy to non-invasive biomarkers in diagnosis and treatment.** Front Med (Lausanne). 2021; 8:615978.

3. Niriella MA, Ediriweera DS, Withanage MY, Darshika S, De Silva ST, de Silva HJ. **Prevalence and associated factors for non-alcoholic fatty liver disease among adults in the South Asian Region: A meta-analysis.** The Lancet Regional Health-Southeast Asia. 2023; 15:1-13.

4. Abbas Z, Saeed A, Hassan SM, Luck NH, Khan A, Zafar MN, et al. **Non-alcoholic fatty liver disease among visitors to a hepatitis awareness programme.** Tropical Gastroenterology. 2014; 34(3):153-8.

5. Marušić M, Paić M, Knobloch M, Liberati Pršo AM. **NAFLD, insulin resistance, and diabetes mellitus type 2.** Can J Gastroenterol Hepatol. 2021; 2021(1):6613827.

6. Paradies G, Paradies V, Ruggiero FM, Petrosillo G. **Oxidative stress, cardiolipin and mitochondrial dysfunction in nonalcoholic fatty liver disease.** World Journal of Gastroenterology: WJG. 2014; 20(39):14205.

7. Makri ES, Makri E, Polyzos SA. **Combination therapies for nonalcoholic fatty liver disease.** J Pers Med. 2022; 12(7):1166.

8. Sanyal AJ, Chalasani N, Kowdley K V, McCullough A, Diehl AM, Bass NM, et al. **Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis.** New England Journal of Medicine. 2010; 362(18):1675-85.

9. Sanyal AJ, Chalasani N, Kowdley K V, McCullough A, Diehl AM, Bass NM, et al. **Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis.** N Engl J Med [Internet]. 2010 May 6 [cited 2024 Apr 9]; 362(18):1675-85. Available from: https://pubmed.ncbi.nlm.nih.gov/20427778/

10. Salvoza NC, Klinzing DC, Gopez-Cervantes J, Baclig MO. **Association of circulating serum miR-34a and miR-122 with dyslipidemia among patients with non-alcoholic fatty liver disease.** PLoS One. 2016; 11(4):e0153497.

11. Engin A. **Non-alcoholic fatty liver disease.** Obesity and Lipotoxicity. 2017; 443-67.

12. Pouwels S, Sakran N, Graham Y, Leal A, Pintar T, Yang W, et al. **Non-alcoholic fatty liver disease (NAFLD): A review of pathophysiology, clinical management and effects of weight loss.** BMC Endocr Disord. 2022; 22(1):63.

13. Henson JB, Simon TG, Kaplan A, Osganian S, Masia R, Corey KE. **Advanced fibrosis is associated with incident cardiovascular disease in patients with non‐alcoholic fatty liver disease.** Aliment Pharmacol Ther. 2020; 51(7):728-36.

14. Feldstein AE. **Novel insights into the pathophysiology of nonalcoholic fatty liver disease.** In: Seminars in liver disease. © Thieme Medical Publishers. 2010; 391-401.

15. Haas JT, Francque S, Staels B. **Pathophysiology and mechanisms of nonalcoholic fatty liver disease.** Annu Rev Physiol. 2016; 78(1):181-205.

16. Vancells Lujan P, Vinas Esmel E, Sacanella Meseguer E. **Overview of non-alcoholic fatty liver disease (NAFLD) and the role of sugary food consumption and other dietary components in its development.** Nutrients. 2021; 13(5):1442.

17. Barb D, Portillo-Sanchez P, Cusi K. **Pharmacological management of nonalcoholic fatty liver disease.** Metabolism. 2016; 65(8):1183-95.

18. Elhence A, Shalimar. **Treatment of non-alcoholic fatty liver disease—Current perspectives.** Indian Journal of Gastroenterology. 2020; 39(1):22-31.

19. Perumpail BJ, Li AA, John N, Sallam S, Shah ND, Kwong W, et al. **The Role of Vitamin E in the Treatment of NAFLD.** Diseases. 2018; 6(4):86.

20. Al-Baiaty FDR, Ismail A, Abdul Latiff Z, Muhammad Nawawi KN, Raja Ali RA, Mokhtar NM. **Possible hepatoprotective effect of tocotrienol-rich fraction vitamin E in non-alcoholic fatty liver disease in obese children and adolescents.** Front Pediatr. 2021; 9:667247.

AUTHORSHIP AND CONTRIBUTION DECLARATION

No.	Author(s) Full Name	Contribution to the paper	Author(s) Signature
1	Muhammad Owais Fazal	Conception of idea writing manuscript.	
2	Ghulam Abbas Tahir	Writing result & discussion.	
3	Yasir Yaqoob	Data collection & complication.	
4	Ahmad Zeeshan	Data collection & complication.	
5	Rabia Sharif	Data collection & complication.	
6	M. Usman Musharraf	Proofreading, Ethical consideration.	