SOCIAL SCIENCE REVIEW ARCHIVES
ISSN Online: 3006-4708
ISSN Print: 3006-4694
https://policyjournalofms.com

Impact of Oral Hypoglycemic Drugs on Complications in NAFLD Patients with Type 2 Diabetes Mellitus

Ayesha Afzal[1], Muhammad Ahmad Raza[2] (Corresponding Author), Ubaid Ur Rehman[3], Muhammad Muneeb[4], Dr. Muhammad Wasil Rehman[5], Sidra Ghazanfar[6]

[1]College of Allied Health Sciences Akhtar Saeed Medical & Dental College Canal Campus, Lahore, Pakistan, Email: vinisheikh8588@gmail.com

[2] MSDU, University institute of radiological sciences & MIT, University of Lahore, Lahore, Pakistan, ORCID: 0009-0002-2932-8424, Email: dr.ahmad663@gmail.com

[3] Lab Scientist, Azra Naheed Medical College, Lahore, Pakistan, Email: ubaidm704@gmail.com

[4] Riphah institute of pharmaceutical sciences, Riphah international university, Lahore, Email: muhammad.muneeb@riphah.edu.pk

[5] Institute of Public Health and Social sciences, Khyber Medical University, Peshawar, Pakistan, Email: muhammadwasilrehman@gmail.com

[6] BSMUT* Student, University institute of radiological sciences & MIT, University of Lahore, Lahore, Pakistan, Email: sidraghazanfar1@gmail.com

Abstract

Objective: To determines prevalence of non-alcoholic fatty liver disease and the impact of lifestyle adjustments and oral hypoglycemic medications on lowering liver enzyme levels and fatty liver alterations.

Material and Method: This comparative, observational study involved patients of both genders with elevated liver enzymes and ultrasound findings of fatty liver changes along with elevated HbA1c, transaminases, total cholesterol (TC), and TGs. It was conducted from November 2022 to May 2023 at the Department of Pharmacy, University of Lahore, Lahore, Pakistan Convenience sampling was used to increase the sample. Individuals with hemochromatosis, liver cancer, bile duct illness, hepatitis, jaundice, Wilson's disease, and alcoholism were not allowed to participate. The diabetic outpatient department (OPD) contacted patients who complained of nausea, anorexia, elevated BMI, and T2DM or not. The patients were recommended to have an ultrasound to rule out sonographic fatty liver abnormalities and a blood test to examine liver enzyme levels after providing written informed permission.

Results: Out of 300 patients, there were 220 females and 80 males. The average age of all individuals was 45±18 years. Table 1 shows that 60 patients (20%) solely had fatty liver alterations, while 240 patients (80%) combined NAFLD with T2DM. Patients with type 2 diabetes mellitus (T2DM) and non-alcoholic fatty liver disease (NAFLD) together and NAFLD alone are characterized in (Table 1). Groups A, B, C, D, E, F, 90 (30%), 30 (10%) patients, 50 (17%), 40 (13.3%%), 30 (10%) and 60 (20%) patients. Table 2 shows that 75 patients (25%) showed post-intervention improvement, with 90 patients (30%) in group A.

Conclusion: OHDs can be used to treat fatty liver, although individuals receiving empagliflozin with metformin treatment showed the greatest improvement, followed by those receiving metformin alone.
Keywords: Type 2 diabetes mellitus, Non-alcoholic fatty liver disease, Metformin

Introduction

A major global health problem, non-alcoholic fatty liver disease (NAFLD) is defined by aberrant fat deposition in the liver cells [1]. If there is no excessive alcohol consumption, the development of NAFLD can begin with simple steatosis (NAFLD), progress to non-alcoholic steatohepatitis (NASH), and ultimately result in cirrhosis and hepatocellular carcinoma. In industrialized countries, NAFLD is one of the primary causes of chronic liver disease. The American Association for the Study of Liver Disease Guidelines state that liver biopsies are the gold standard for diagnosing nonalcoholic fatty liver disease (NAFLD); however, due to the high cost and increased health risks involved, ultrasonography is more frequently used, especially in developing countries[2]. Liver disease advances due to intricate interactions between the parenchymal and nonparenchymal cells that exist in the liver, as well as the immune cells that are drawn to the liver in reaction to damage[3]. The risk of hepatic injury is increased by liver illness linked to type 2 diabetes mellitus (T2DM), elevated body mass index (BMI), and spike in triglyceride (TG) levels as well as heart-related conditions. Despite having first afflicted Western nations, NAFLD has now been documented in poorer countries like Pakistan. The individuals may experience severe fatty liver alterations that manifest as liver inflammation, cirrhosis, and liver failure[4]. Another research study found that 56% of individuals with T2DM who also had high ALT levels and liver biopsy results had non-alcoholic fatty liver disease. In another research, the prevalence rate was 75% among 26 individuals with type 2 diabetes.3 Among T2DM patients with high glycated hemoglobin (HbAIc) levels who have been diagnosed, the incidence of NAFLD has typically varied from 35 to 72%[5]. The relationships between T2DM and NAFLD are reciprocal in nature. The development of NAFLD and cardiac problems is associated with both obesity and type 2 diabetes separately. A increased risk of liver cirrhosis and hepatocellular carcinoma (HCC) as well as a higher death rate are experienced by individuals with a baseline diagnosis of NAFLD and T2DM. Increased hepatic glucose production and impaired insulin sensitivity are markers of non-alcoholic fatty liver disease (NAFLD), and the buildup of certain lipids in the liver can impact insulin signally. Future risk of acquiring type 2 diabetes is strongly correlated with elevated transaminase levels. Therefore, the chance of acquiring type 2 diabetes is raised by more than two times in people with NAFLD [6]. Oral hypoglycemic medications have been suggested as a treatment for NAFLD because to the intricate link between NAFLD and T2DM.Given the connections between T2DM and NAFLD, treating NAFLD as a metabolic illness may benefit from a comprehensive strategy that emphasizes addressing hepatic lipid alterations, hyperglycemia, and insulin sensitivity. Even in the absence of cirrhosis, a high rate of HCC has been noted in these individuals. Sung et al. discovered that a twofold risk of acquiring type 2 diabetes was linked to obesity, insulin resistance (IR), and ultrasound-diagnosed non-alcoholic feeding syndrome (NAFLD). This cohort study included approximately 12,000 South Korean people. The chance of having T2DM rose by around 14 times when all three risk variables were present at the same time [7]. Numerous researches have demonstrated a connection between NAFLD and a nearly twofold increased incidence of type 2 diabetes, which can result in liver fibrosis and hepatic steatosis.

Combining the available data with bias analysis, it has been determined that people with NAFLD have a greater chance of developing type 2 diabetes (T2DM), which implies a causal relationship between NAFLD and T2DM [8].

Research has also indicated that people with NAFLD and T2DM, including those in low to normal body mass index (BMI) categories, have an elevated risk of cardiovascular diseases. Complications from fatty liver diseases that go untreated include oesophageal varicose, ascites, enlarged spleen, hepatic encephalopathy, liver cancer, and liver failure. Elevated blood pressure (BP) is associated with increased levels of TG and low-density lipoprotein (LDL), which in turn increases the risk of cardiovascular diseases by way of dyslipidemia, hypertension (HTN), and a higher incidence of type 2 diabetes (T2DM)[9]. The goal of treating NAFLD with lifestyle modification and OHDs is to reduce blood glucose levels, BMI, and address the underlying pathophysiological pathways shared by T2DM and NAFLD. One of these processes is adipose tissue malfunction, which is linked to both IR and obesity[10]. Anti-hyperglycemic medication is used to control glucose metabolism and increase insulin sensitivity, demonstrating the links between T2DM and NAFLD. Research has demonstrated that OHDs, such as metformin, agonists of the glucagon-like peptide-1 (GLP-1) receptor, and inhibitors of the sodium glucose co-transporter-2 (SGLT-2) are beneficial in promoting weight reduction and lowering body mass index (BMI)[11]. So, since T2DM and NAFLD jointly accelerate the development of fatty liver alterations, it is critical to treat both conditions. For the time being, NAFLD patients have been treated with lifestyle changes and glucose-lowering medications such as SGLT2 inhibitors, GLP-1R agonists, and PPAR agonists[12]. In people with type 2 diabetes who do not have complications from their disease, metformin is widely used to reduce blood glucose levels. Mainly by modest weight loss and hepatic gluconeogenesis inhibition, metformin achieves its therapeutic goals. Yet, there is conflicting evidence about metformin's impact on NAFLD. When treating type 2 diabetes, metformin is an often advised and efficient drug. HbA1c levels are also lowered by around 0.5% to 1%, and it is regarded as safe[13]. Treatment for type 2 diabetes is achieved using SGLT2 inhibitors. In patients with type 2 diabetes, they lower the risk of cardiovascular illnesses by decreasing the reabsorption of glucose from the kidneys through the renal tubules, which lowers bodyweight and hyperglycemia. These effects on NAFLD have been demonstrated to be advantageous for SGLT2 inhibitors[14].

The incretins GLP-1 and glucose-dependent insulin tropic peptide (GIP) are inhibited by dipeptidyl-peptidase IV (DPP-4) inhibitors, which also lower blood glucose levels, enhance insulin secretion, decrease stomach emptying, and suppress glucagon release. It is unknown if DPP-4 inhibitors reduce bodyweight or enhance cardiovascular outcomes in NAFLD patients[15]. The goal of the current investigation was to ascertain the frequency of fatty liver disease in people with type 2 diabetes and the effects of OHD medication and lifestyle change in lowering hepatic enzyme levels and fatty alterations in the liver.

Material and Method

This comparative, observational study involved patients of both genders with elevated liver enzymes and ultrasound findings of fatty liver changes along with elevated HbA1c, transaminases, total cholesterol (TC), and TGs. It was conducted from November 2022 to May 2023 at the Department of Pharmacy, University of Lahore, Lahore, Pakistan Convenience sampling was used to increase the sample. Individuals with hemochromatosis, liver cancer, bile duct illness, hepatitis, jaundice, Wilson's disease, and alcoholism were not allowed to participate.

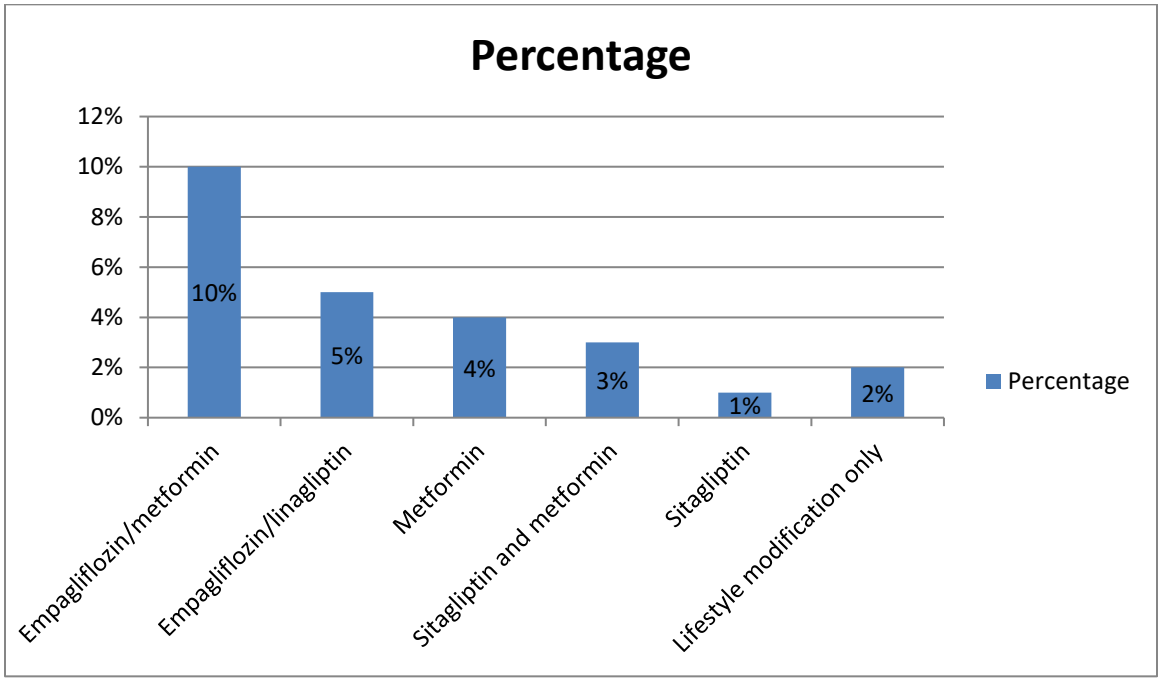
The diabetic outpatient department (OPD) contacted patients who complained of nausea, anorexia, elevated BMI, and T2DM or not. The patients were recommended to have an ultrasound to rule out sonographic fatty liver abnormalities and a blood test to examine liver enzyme levels after providing written informed permission. The blood tests that were recommended were the HbA1C, TC, SG, urine glucose test, and serum glutamic pyruvic transaminase and glutamic-oxaloacetic transaminase. The endocrinologist then gave the subjects prescriptions for OHDs. Every patient referred by the endocrinologist was subjected to an ultrasound by the sonologist in the radiology section. The abdomen was ultrasonically cleaned using a GE-20 ultrasound machine after a fast of six to eight hours. Using a 2.5–3.5MHz convex probe (curvilinear transducer), the patients were in a supine posture, and the liver and gall bladder could be viewed. In both genders, liver size up to 15 cm and up to 16 cm was considered normal. Beyond that, the eco-texture of the liver was examined to determine whether or not it was hyperechoic. A higher hepatic echogenicity in NAFLD patients suggested a fatty infiltration of the liver. These individuals were fasted for 12 hours prior to having blood samples taken. Fatty stated that they were then sent back to the endocrinologist for an OHD prescription as well as the liver enzyme levels. Group A received empaglifazolin+metformin, Group B received empaglifazolin+linglaptin, Group C received sitaglaptin+metformin, Group D received metformin alone, and Group E received sitaglaptin alone. All treatment groups received advice on lifestyle adjustments, whereas control group F received simply that advice. Three months were spent on the intervention. At the conclusion of the intervention, baseline studies were conducted once more. SPSS 25 was used to analyze the data. The mean±standard deviation was calculated using descriptive statistics. Using the t-test, inferential statistics were employed. Significant data was defined as $P<0.05$.

Table1: Patients Data

Characters	**Fatty liver with T2DM n=240**	**Fatty liver with T2DM n=60**	**P-value**
Age			
18-40	60	13	>0.05
41-60	154	40	
61-80	26	7	
Gender			
M=80	60	20	>0.05
F=220	147	73	
Lipid Profile			
Cholesterols	204 ±4	205 ±7	>0.05
Triglycerides	135±5	75 ±6	
LFT			
SGPT	155±6	1 ±4	>0.05
SGOT	55 ±6	40 ±4	
USG Scan			
Grade I	80	40	>0.001
Grade II	160	20	
Mean BMI	32 ±6	20±2	>0.001
T2DM HbA1C	240	60	>0.001

Table 2: Post Interventions (n=300)

Therapy	No. of Patients	Ultrasound Grad-I
Empagliflozin/metformin	90	30 (10%)
Empagliflozin/linagliptin	30	15 (5%)
Metformin	50	12(4%)
Sitagliptin and metformin	40	9 (3%)
Sitagliptin	30	3(1%)
Lifestyle modification only	60	6(2%)
Total	**300**	**75(25%)**



Results

Out of 300 patients, there were 220 females and 80 males. The average age of all individuals was 45±18 years. Table 1 shows that 60 patients (20%) solely had fatty liver alterations, while 240 patients (80%) combined NAFLD with T2DM. Patients with type 2 diabetes mellitus (T2DM) and non-alcoholic fatty liver disease (NAFLD) together and NAFLD alone are characterized in (Table 1). Groups A, B, C, D, E, F, 90 (30%), 30 (10%) patients, 50 (17%), 40 (13.3%%), 30 (10%) and 60 (20%) patients. Table 2 shows that 75 patients (25%) showed post-intervention improvement, with 90 patients (30%) in group A.

Discussion

The current investigation included 200 individuals with NAFLD diagnoses, including both genders, of them, 60(20%) had pre-diabetes, and 240(80%) developed type 2 diabetes. Metformin with empagliflozin substantially improved liver enzyme levels, TG, and BMI. Numerous research works have demonstrated the heightened correlation between type 2 diabetes (T2DM) and non-alcoholic fatty liver disease (NAFLD), with obesity playing a major impact in elevating the likelihood of cardiovascular disorders among affected individuals[16-18]. Research using sitagliptin or vildagliptin, DPP-4 inhibitors, as a treatment for non-alcoholic fatty liver in

diabetics did not significantly reduce fatty liver abnormalities or HbAIc. Another study (18) shown that BMI, TG, LDL levels, and fatty liver alterations decreased after three months of treatment. Studies have shown that NAFLD is on the rise, with OHDs being the recommended course of therapy. According to other reports, insulin secretagogues and lifestyle changes have a real positive impact on the treatment of disease. A research that compared low-bodyweight NAFLD patients with obese or overweight individuals found that 20% of patients also had high scores for fibrosis and carotid atherosclerosis. For these individuals,OHDs were the best at reducing body weight, HbAIC, and BMI[19-21]. According to a research, the combination of metformin and empagliflozin lowered overweight, IR, BMI, and HbAIc with improved results[22].

Conclusion

OHDs can be used to treat fatty liver, although individuals receiving empagliflozin with metformin treatment showed the greatest improvement, followed by those receiving metformin alone.

References

1. Ashtari S, Pourhoseingholi MA, Zali MR. Non-alcohol fatty liver disease in Asia: Prevention and planning. World journal of hepatology. 2015 Jul 7;7(13):1788.
2. Lombardi R, Onali S, Thorburn D, Davidson BR, Gurusamy KS, Tsochatzis E. Pharmacological interventions for non-alcohol related fatty liver disease (NAFLD). Cochrane Database of Systematic Reviews. 2017(3).
3. Miyata T, Wu X, Fan X, Huang E, Sanz-Garcia C, Cajigas-Du Ross CK, Roychowdhury S, Bellar A, McMullen MR, Dasarathy J, Allende DS. Differential role of MLKL in alcohol-associated and non–alcohol-associated fatty liver diseases in mice and humans. JCI insight. 2021 Feb 2;6(4).
4. Anstee QM, Targher G, Day CP. Progression of NAFLD to diabetes mellitus, cardiovascular disease or cirrhosis. Nature reviews Gastroenterology & hepatology. 2013 Jun;10(6):330-44.
5. Seetlani NK, Memon AR, Tanveer S, Ali A, Ali P, Imran K, Haroon H. Frequency of non-alcoholic steatohepatitis on histopathology in patients of type 2 diabetes mellitus with duration of more than 5 years. J Coll Physicians Surg Pak. 2016 Aug 1;26(8):643.
6. Targher G, Corey KE, Byrne CD, Roden M. The complex link between NAFLD and type 2 diabetes mellitus—mechanisms and treatments. Nature reviews Gastroenterology & hepatology. 2021 Sep;18(9):599-612.
7. Sung KC, Yoo TK, Lee MY, Byrne CD, Zheng MH, Targher G. Comparative Associations of Nonalcoholic Fatty Liver Disease and Metabolic Dysfunction–Associated Fatty Liver Disease With Coronary Artery Calcification: A Cross-Sectional and Longitudinal Cohort Study. Arteriosclerosis, Thrombosis, and Vascular Biology. 2023 Mar;43(3):482-91.
8. Ishido S, Tamaki N, Takahashi Y, Uchihara N, Suzuki K, Tanaka Y, Miyamoto H, Yamada M, Matsumoto H, Nobusawa T, Keitoku T. Risk of cardiovascular disease in lean patients with nonalcoholic fatty liver disease. BMC gastroenterology. 2023 Jun 17;23(1):211.
9. Lu H, Zeng L, Liang B, Shu X, Xie D. High prevalence of coronary heart disease in type 2 diabetic patients with non-alcoholic fatty liver disease. Archives of Medical Research. 2009 Oct 1;40(7):571-5.

10. Ezpeleta M, Gabel K, Cienfuegos S, Kalam F, Lin S, Pavlou V, Song Z, Haus JM, Koppe S, Alexandria SJ, Tussing-Humphreys L. Effect of alternate day fasting combined with aerobic exercise on non-alcoholic fatty liver disease: A randomized controlled trial. Cell metabolism. 2023 Jan 3;35(1):56-70.
11. Rashid A, Zafar S, Bashir A, Bakht K, Bhalli AU. Presence of non-alcoholic fatty liver disease in patients of uncontrolled and controlled type 2 diabetes mellitus. Pakistan Armed Forces Medical Journal. 2019 Aug 27;69(4):822-25.
12. Bianchi C, Miccoli R, Daniele G, Penno G, Del Prato S. Is there evidence that oral hypoglycemic agents reduce cardiovascular morbidity/mortality? Yes. Diabetes care. 2009 Nov;32(Suppl 2):S342.
13. Garg S, Mallik D. Role of Vitamin D as an Adjuvant to Oral Hypoglycemic Drugs in Treatment of Type-2 Diabetic Patients. Asian Journal of Medical Sciences. 2020 Feb 29;11(2):25-9.
14. Avery MA, Mizuno CS, Chittiboyina AG, Kurtz TW, Pershadsingh HA. Type 2 diabetes and oral antihyperglycemic drugs. Current medicinal chemistry. 2008 Jan 1;15(1):61-74.
15. Cui J, Philo L, Nguyen P, Hofflich H, Hernandez C, Bettencourt R, Richards L, Salotti J, Bhatt A, Hooker J, Haufe W. Sitagliptin vs. placebo for non-alcoholic fatty liver disease: a randomized controlled trial. Journal of hepatology. 2016 Aug 1;65(2):369-76.
16. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease—meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016 Jul 1;64(1):73-84.
17. De Vries M, Westerink J, Kaasjager KH, De Valk HW. Prevalence of nonalcoholic fatty liver disease (NAFLD) in patients with type 1 diabetes mellitus: a systematic review and meta-analysis. The Journal of Clinical Endocrinology & Metabolism. 2020 Dec;105(12):3842-53.
18. Tilg H, Moschen AR, Roden M. NAFLD and diabetes mellitus. Nature reviews Gastroenterology & hepatology. 2017 Jan;14(1):32-42.
19. Lin YH, Zhang ZJ, Zhong JQ, Wang ZY, Peng YT, Lin YM, Zhang HP, Tian JQ. Semaglutide combined with empagliflozin vs. monotherapy for non-alcoholic fatty liver disease in type 2 diabetes: Study protocol for a randomized clinical trial. Plos one. 2024 May 3;19(5):e0302155.
20. Tan DJ, Ng CH, Lin SY, Pan XH, Tay P, Lim WH, Teng M, Syn N, Lim G, Yong JN, Quek J. Clinical characteristics, surveillance, treatment allocation, and outcomes of non-alcoholic fatty liver disease-related hepatocellular carcinoma: a systematic review and meta-analysis. The Lancet Oncology. 2022 Apr 1;23(4):521-30.
21. dos Santos LR, Duarte ML, Peccin MS, Gagliardi AR, Melnik T. Dipeptidyl peptidase IV inhibitors for nonalcoholic fatty liver disease-systematic review and metanalysis. Current Diabetes Reviews. 2021 Jun 1;17(5):70-81.
22. Caturano A, Galiero R, Loffredo G, Vetrano E, Medicamento G, Acierno C, Rinaldi L, Marrone A, Salvatore T, Monda M, Sardu C. Effects of a combination of empagliflozin plus metformin vs. metformin monotherapy on NAFLD progression in type 2 diabetes: the IMAGIN pilot study. Biomedicines. 2023 Jan 23;11(2):322.