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Preventing NASH with Empagliflozin and Linagliptin: A Diabetic Drug Combination

Asma Abdul Razzak, Pervez Ashraf

ABSTRACT:

Objective: To determine the effect of anti-diabetic drug combination of 25mg empagliflozin and 5mg linagliptin for the prevention of NASH.

Study Design & Setting: Quasi-Experimental Study design, Department of Gastroenterology, Medicare Cardiac and General Hospital Karachi from October 2022 to March 2023.

Methodology: This study was carried out after approval from the ethical board of the hospital. The selection criteria of patients included positive family history of obesity, hyperlipidemia/ hypertriglyceridemia, hypothyroidism, smoking and F3 Fibrosis on transient elastography. The initial screening of clinical history, physical examination, laboratory findings were recorded after taking the written consent from each patient. The baseline findings were recorded and the effect of drugs was examined after follow-up of six months.

Results: The study included 150 patients who received the treatment of empagliflozin and linagliptin. The mean age of these patients was 37±4.9 years. Majority of them were males 76% and 60% were diagnosed type 2 diabetes more than 5 years ago. Hyperglycemia and hypoglycemia were found in 16.7% in patients with headache of 26.7%. The baseline findings were significantly changed with effective and favorable results as p-value<0.001.

Conclusion: The treatment with combine effect of the antidiabetic drugs empagliflozin (25 mg) and linagliptin (5 mg) showed a safety profile of preventing NASH with the fixed dose. It reduced the ALT and AST levels, reduced BMI, triglyceride level, HBA1C and the risk of progression of advance liver disease NASH. After taking antidiabetic drugs, Fibrosis was improved and it showed F1–F2 on transient elastography.

Keywords: Anti-diabetic drugs, Non-alcoholic fatty liver disease, Non-alcoholic steatohepatitis.

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INTRODUCTION:

Non-alcoholic steatohepatitis (NASH) is a progressive form of non-alcoholic fatty liver disease (NAFLD). Increase of fat in the liver is the root cause of NAFLD and when it damages and inflames the liver, it results in NASH, which can cause liver scarring. The prevalence of NAFLD and NASH is reported in different research with an abundance of diversity.[1] The prevalence of non-alcoholic fatty liver disease (NAFLD), which affects an estimated one-fourth of adults globally, has made it a severe public health issue. According to estimates, 3-5% of the world's population suffers NASH, with the majority experiencing several comorbidities. Clinical outcomes are influenced by progressing fibrosis, 20% of patients will develop cirrhosis and/or HCC, with the latter being the main cause of death in NASH.[2] Up to 30% of NAFLD patients develop non-alcoholic steatohepatitis (NASH), which is characterized by hepatic lipid deposition (steatosis), lobular inflammation, hepatocellular ballooning, and fibrosis. NAFLD and NASH both have a 25.2% and a 1.5–6.45% global prevalence, respectively.[3] The chances of developing NASH rises with age. It is still not entirely identified how gender variations affect the likelihood of developing NASH.[4]

NASH and diabetes mellitus are two distinct yet closely interconnected metabolic disorders that have garnered significant attention due to their escalating global prevalence and their intricate impact on human health. Due to its strong association with diabetes and its potential to elevate the risk of serious complications such as hepatocellular carcinoma (HCC) and cirrhosis, NASH can be referred to as "Diabetic Liver Disease".[5] The changes in glucose and lipid metabolism, insulin resistance (IR), and insulin secretion are the key pathophysiological mechanisms driving the development of NAFLD, which accounts for the strong relationship between NAFLD and Type 2 diabetes.[6] In Japan, type 2 diabetes (T2D) mortality is mostly triggered by liver disorders,

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accounting for 9.3% of all deaths. The strong interconnection between nonalcoholic fatty liver disease (NAFLD) and type 2 diabetes (T2D) underscores their status as two of the most prevalent chronic health conditions worldwide. NAFLD, a widely prevalent liver ailment and T2D, a common metabolic disorder, are intricately linked, showcasing a substantial relationship between these two health issues.[7]

The importance of vitamin E as a fundamental therapy option, particularly for people without diabetes, has been shown by extensive research and clinical investigations. With patients who have severe fibrosis, this therapeutic approach has shown tremendous promise in preventing the course of liver disease. The importance of this approach rests in its capacity to stop liver problems from progressing to critical stages that could cause hepatic decompensation or require transplantation.[8] Vitamin E, a fat-soluble antioxidant, plays a vital role in protecting cells from oxidative stress and inflammation. In the context of nonalcoholic fatty liver disease (NAFLD) and its more advanced form, nonalcoholic steatohepatitis (NASH), oxidative stress and inflammation are key contributors to disease progression. Severe fibrosis represents a critical stage in the progression of NAFLD and NASH, often associated with increased risk of liver-related complications. Vitamin E by itself had no discernible effect on the key histology result in T2D patients with NASH. Combination of vitamin E and pioglitazone is more effective than a placebo for enhancing liver histology in NASH patients with diabetes.[9] Metformin remains the recommended first-line treatment for type 2 diabetes, even though its direct impact on NAFLD and NASH might be limited. Its well-established benefits in diabetes management, safety profile and potential ancillary advantages make it a valuable tool in the comprehensive approach to treating individuals with type 2 diabetes.[10-12]

The synergistic approach of combining linagliptin with empagliflozin, complemented by a balanced and nutritious diet, and consistent physical activity, forms a comprehensive strategy to effectively manage elevated blood sugar levels associated with diabetes. Linagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor, aids in maintaining stable blood sugar levels by inhibiting the breakdown of incretin hormones which stimulate insulin release and suppress glucagon secretion. Empagliflozin, on the other hand, is a sodium-glucose co-transporter 2 (SGLT2) inhibitor that promotes the elimination of excess glucose through urine, reducing its reabsorption in the kidneys.

This combination leverages the distinct mechanisms of action of linagliptin and empagliflozin to target multiple aspects of glucose regulation within the body. Additionally, it helps individuals with type 2 diabetes, heart disease, and blood vessel disease reduce their risk of mortality. In the kidneys, empagliflozin helps to stop the absorption of glucose, the blood sugar. By raising the amounts of chemicals in the body that cause the pancreas to produce more insulin, linagliptin aids with blood sugar regulation. When there is excessive sugar in the blood, it also warns the liver to stop generating sugar.[13] By eating a balanced diet and keeping a healthy weight, people may be able to avoid them. Changing your diet and losing weight may be advised by the doctor if someone is suffering from NAFLD. Research on several diseases and conditions is conducted and supported by the National Institutes of Health (NIH), including the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).[14]

Combination therapy of currently available anti-diabetic medications will probably lead to better effectiveness in the future by addressing a variety of key pathways in the development of NASH. If SGLT2 inhibitors are used as the first-line therapy for NASH/NAFLD, there is a risk that this will worsen the condition since hyperglucagonemia can play significant roles in the etiology of the disease. This experimental study aimed to determine the effect of anti-diabetic drug combination of empagliflozin and linagliptin for the prevention of NASH. This research will explore the indirect prevention of treating chronic liver disease NAFLD and to prevent NASH.

METHODOLOGY:

A quasi-experimental study was systematically undertaken at the Medicare Cardiac and General Hospital located in Karachi. Prior to the initiation of the study, ethical approval was diligently sought and obtained from the relevant ethical review board, ensuring that the research adhered to established ethical standards and guidelines. The data collection period spanned from October 2022 to March 2023, encompassing a duration of six months. During this time, diabetic patients who also presented with liver disease were identified and included as participants in the study. The criteria used for the selection of patients encompassed several key factors. These factors included the presence of F3 Fibrosis as determined through transient elastography, a positive family history of obesity, an elevated Body Mass Index (BMI) exceeding 25, the presence of hyperlipidemia or hypertriglyceridemia, a diagnosis of hypothyroidism, a history of smoking, and a lifestyle characterized by physical inactivity and sedentary habits. The parameters guiding the exclusion of participants were meticulously defined to ensure the integrity of the findings of the study. Pregnant women, due to the unique physiological state of pregnancy, were purposefully omitted from the participant to maintain a focused investigation on the selected variables. Similarly, individuals grappling with malignancy, sepsis, pancreatitis and allergies were excluded from the study. The calculated sample size by using Openepi and keeping 95% confidence interval was 17 from the study . They reported that 1.1% patients will suffer from liver disease by taking the combination of empagliflozin + linagliptin. The sample size will be increased up to 150 to precise the results.

The initial screening of clinical history, physical examination, laboratory findings and HBA1C of more than 9% were recorded after taking the written consent from each patient. The antidiabetic drug used in the study was the combination of empagliflozin and linagliptin. The study medicines were given as per the routine administration policy by the primary author. The baseline findings were recorded and the effect of drugs was examined after follow-up of six months.

IBM SPSS version 21.0 and Microsoft Excel 2013 were employed as the analytical platforms. For continuous variables, such as age, the analysis hinged on utilizing the mean accompanied by its corresponding standard deviation (SD). Numbers with percentages was used for categorical variables such as gender, group etc. The pre/post analysis was undertaken using the paired t-test, a statistical method adept at assessing the significance of differences within paired data points and the significance was determined by the p-value, with a threshold set at less than 0.05.

RESULTS:

The research involved a total of 150 diabetic patients who underwent treatment using both empagliflozin and linagliptin. The average age of these patients was calculated to be 37 years, with a standard deviation of 4.9 years. The age range spanned from 22 to 45 years. A notable predominance of male patients was observed, with 114 individuals (76%), while the remaining 36 patients (24%) were female. The average BMI of patients was 27.5±1.6 with the majority lied between 25 and 30. 60% were diagnosed type 2 diabetes more than 5 years ago.

Within the spectrum of adverse events, the recorded occurrences encompassed instances of both hyperglycemia and hypoglycemia with 25 cases (16.7%). A noteworthy observation emerged, indicating that the predominant adverse reaction among the participants was headache, with a substantial 40 instances (26.7%) reported. Almost half of the patients were not taking concomitant oral anti-diabetic drugs.

Table 1 presents the treatment effects of a combination of anti-diabetic drugs before and after intervention. The baseline findings of all the 150 patients were presented in detail which showed significantly changed with effective and favorable results as p-value<0.05.

The p-values indicated that the observed changes in all these parameters are statistically significant, implying that the intervention had a notable impact on these measures. The table succinctly presents the quantitative changes in these parameters before and after the anti-diabetic drug combination intervention, showcasing the effectiveness of the treatment.

DISCUSSION:

Recent research has revealed a strong, reciprocal link between diabetes and NASH. Despite the complexity of the relationship between these things, a number of fundamental mechanisms have been put forth that include common pathophysiological processes such adipokine dysregulation, oxidative stress, inflammation, and insulin resistance. World Health Organization (WHO) should be evaluated for NASH-fibrosis for the current guidelines[16,17] as it is still unclear. Despite suggesting "consider screening" in cases of high risk patients, such as those with obesity and metabolic syndrome or type 2 diabetes, they oppose systematic screening due to the knowledge gaps regarding the cost-effectiveness of this method. It is understandable that there is a conflicting message regarding screening and intervention because there is insufficient information on how early intervention affects the course of steatohepatitis.[18] There is a critical need for novel insulin sensitizers because the pathophysiology of both T2D and NASH is largely influenced by insulin resistance. Although Peroxisome proliferator-activated receptor (PPAR) agonists, particularly PPARy and pan-PPARs agonists have demonstrated some positive benefits on both NASH and liver fibrosis. The frequent use of these agents should be constrained by their safety profile. The most effective anti-diabetic medications for NASH treatment are incretin-based therapies, such as glucagon-like peptide 1 receptor agonists (GLP-1 RAs) and the polyagonists (GLP-1, GIP, and glucagon) currently being developed. This is mainly because of the way these medications affect body weight loss.

Table 1: Treatment Effects of Anti-Diabetic Drug Combination.

	Before intervention	After intervention	p-value*
ALT	94.5±9.1	68.01±7.6	<0.001
AST	86.05±9.0	75.2±3.2	<0.001
Triglyceride	249.04±29.3	174.6±42.1	<0.001
HBA1C	8.04±1.3	6.5±0.5	<0.001
TSH	13.7±1.9	11.0±1.4	<0.001
BMI (kg/m^2)	27.5±1.6	21.6±1.8	<0.001

*Significant value by paired sample t-test. [ALT: Alanine Transaminase, AST: Aspartate Aminotransferase, BMI: Body Mass Index, TSH: Thyroid Stimulating Hormone]

Fibroblast growth factor (FGF)19 and FGF21-based treatments, as well as SGLT2 inhibitors, appear to be potential targets for the treatment of NASH and type 2 diabetes. Due to short-term randomized trials, all of these medications have the limitation of having a limited impact on liver fibrosis.[19] Pioglitazone has been proven to alleviate the histological characteristics of NASH among anti-diabetic medications. The impact of more modern anti-diabetic medications, such as dipeptidyl peptidase 4 inhibitors (DPP-4i), sodium glucose cotransporter 2 inhibitors (SGLT2i), and glucagon-like peptide-1 receptor agonists (GLP-1 RAs), on NAFLD/NASH have lately drawn more attention.[20]

Peroxisome proliferator-activated receptor agonists, sodium-dependent glucose cotransporter inhibitors, and glucagon-

like peptide-1 analogues have all been demonstrated to improve metabolic parameters and decrease hepatic lipid buildup and inflammation. But it is necessary to determine how these anti-diabetic medications precisely reverse NASH.[21] Pioglitazone emerges as a particularly compelling candidate among the spectrum of anti-diabetic medications due to its well-established and robust evidence supporting its potential role in treating Nonalcoholic Fatty Liver Disease (NAFLD). The empirical support garnered by pioglitazone underscores its efficacy in managing NAFLD, positioning it as a significant contender in the therapeutic landscape for this condition.[22] One noteworthy aspect is the discernible impact of pioglitazone on liver histology, particularly in individuals diagnosed with biopsy-proven Nonalcoholic Steatohepatitis (NASH). Studies and research endeavors have consistently demonstrated that pioglitazone has the capacity to improve liver histology in these individuals, thereby suggesting its ability to mitigate the inflammation and cellular damage characteristic of NASH. However, it is pertinent to acknowledge that despite pioglitazone's promising attributes, there are considerations that warrant attention. Notably, there may be associated adverse effects or limitations tied to its use, which should be weighed against its potential benefits. This comprehensive assessment is essential for making informed treatment decisions and ensuring the well-being of patients. Shifting focus, while it might still be early to definitively recommend the use of Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RAs) for the treatment of liver disease in NAFLD patients, one specific member of this class, liraglutide, has exhibited encouraging outcomes in this realm.[22]

When used alone or in combination with the effective statin therapy that is advised in T2DM, newer anti-diabetic medications (SPPARMs, GLP-1 RA, and SGLT2i) may significantly contribute to the amelioration of NAFLD/NASH, thereby lowering both liver-specific and cardiovascular morbidity.[23] Empagliflozin alone slows the progression of NASH and has anti-steatotic and anti-inflammatory effects, but when taken with linagliptin, it can effectively slow the progression of NASH and have better anti-fibrotic effects.[24] This study showed that the effect of combined empagliflozin and linagliptin drugs is more effective as compared to alone. It reduced the ALT and AST level along with triglycerides, sugar level as well as hypoglycemia.

Pioglitazone has the best evidence of potential efficacy among the currently available anti-diabetic medications, but there are also significant possible adverse effects, most notably peripheral edoema that might lead to weight gain, that need to be taken into account. However, further information is needed. Liraglutide is also encouraging.[25]

CONCLUSION:

The administration of the combined antidiabetic drugs empagliflozin (25 mg) and linagliptin (5 mg) demonstrated a secure and effective profile in mitigating the risk of Nonalcoholic Steatohepatitis (NASH) through a standardized dosage. This intervention yielded promising outcomes, including notable reductions in both ALT and AST levels, as well as a decrease in BMI, triglyceride levels, and HBA1C. Additionally, the treatment exhibited the potential to curtail the advancement of advanced liver disease NASH, underlining its relevance as a therapeutic strategy.

Remarkably, the utilization of these antidiabetic drugs also led to enhancements in fibrosis, with participants displaying improved fibrosis levels assessed as F1–F2 on transient elastography. Furthermore, the combined treatment exhibited a compelling impact on a key primary outcome, specifically lowering the risk of mortality linked to cardiovascular causes and reducing hospitalizations related to heart failure and kidney disease. These findings collectively highlight the multifaceted positive effects of the empagliflozin and linagliptin combination, positioning it as a promising avenue for addressing NASH and associated complications.

Authors Contribution:
Sana Abdul Razzak: Conception and design
Pervez Ashraf: Manuscript writing, data analysis, interpretation

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