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Original article

Comparison between the effect of Empagliflozin and Pioglitazone added to metformin in patients with type 2 diabetes and nonalcoholic fatty liver disease

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Highlights

- Add-on therapy with Empagliflozin or Pioglitazone with metformin are equally effective in improving liver fibrosis stage and stiffness in T2DM patients with NAFLD.
- Combination of Empagliflozin with metformin is superior to Pioglitazone with metformin in associated with reducing weigh which is main intervention in improving NAFLD.
- Add-on therapy with Empagliflozin or Pioglitazone with metformin are equally reducing total cholesterol, LDL-C and triglyceride levels.

Abstract

Background/aims

Non-alcoholic fatty liver disease (NAFLD), defined as the accumulation of >5% fat in the liver, is the most frequently co-exist disease with diabetics up to 70%. Current study was conducted to compare efficacy of combination therapy of empagliflozin (EMPA) or pioglitazone (PGZ) with metformin (MET) in patients with T2DM and NAFLD.

Methods

In this open label, prospective clinical trial, sixty patients were randomly assigned to receive EMPA 10mg/day or PGZ 30mg/day in combination Metformin (at least 1500mg) for six months. NAFLD grade and liver stiffness were defined and measured at the beginning and after 6 months. As the secondary outcomes, anthropometric characteristics, lipid profile, plasma glucose test, and liver enzymes test were measured at the baseline and endpoint.

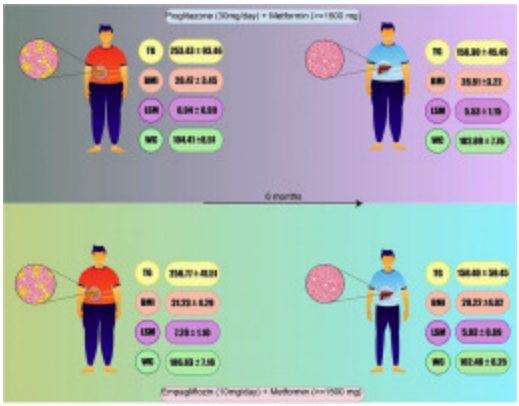
Results

The results showed that both combination therapy with EMPA+ MET or PGZ+MET significantly reversed fibrosis stage of NAFLD (P<0.05). Significant reduction in lipid profile test, and liver enzymes test were seen in both groups (P<0.05). However, the greater reduction in waist circumference was observed in EMPA groups compared to PGZ (-4.4±2.39vs -2.05±1.28, p<0.001), meanwhile weight and BMI decreased significantly only in the patients receiving EMPA (-5.78±3.6kg vs 0.93±0.33kg and -2.01± 3.19kg/m^2 vs 0.33±0.12kg/m^2, respectively, P<0.001).

Conclusion

combination of EMPA or PGZ with metformin equally improved liver fibrosis stage and stiffness in T2DM patients with NAFLD. The improvements of laboratory tests were observed in the both groups, while, regarding weight reduction, only the regimen containing EMPA was effective.

Graphical abstract



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Introduction

Non-alcoholic fatty liver disease (NAFLD) is a chronic hepatic disease that describes the accumulation of fats (>5%) in the liver; which has caused various complications that progressed and resulted in an increment of all-cause mortality. [1] NAFLD, defined as the accumulation of >5% fat in the liver, is characterized by a range of histological spectrum presentation including steatotic, ballooning and inflammation in lobar with or without fibrosis [2]. The prevalence of NAFLD has increased over time and it has affected approximately 25.2–29.8% of the population till 2022, globally [3]. The prevalence of NAFLD in Iran was reported 38.07% which took fifth place from top in Asian countries [4].

Obesity, metabolic syndrome, dyslipidemia and diabetes type 2 (T2DM) are the most important risk factors for NAFLD [5,6] and men have been more affected than women (39·7% vs 25·6%). Various mechanisms are involved in the pathogenesis of NAFLD including insulin resistance, increase in free fatty acids, mitochondrial dysfunction, Iron overload and oxidative stress [7] Particularly, insulin resistance observed in T2DM may lead to hepatic steatotic disease (SLD) through increasing accumulation of free fatty acid in liver. As

mentioned, T2DM is known as a strong risk factor for promoting prevalence of NAFLD and most frequently co-exist disease (according to Rinaldi et al. was peaked up to 70%) [8].

In addition to life style modifications including healthy diet, weight loss, and aerobic exercise at least 150 min per week, iron reduction through phlebotomy, antidiabetic agents are considered as pharmacological intervention to treat NAFLD [9,10]. According to the American and European Associations for the Study of Liver Diseases, Pioglitazone (PGZ) (categorized in thiazolidinedione (TZD) antidiabetic class) approved and recommended in patients with biopsy-proven fibrosis [9,11]. It has been demonstrated that PGZ, as a PPAR-agonist, ameliorates SLD and attenuates liver fibrosis [12]. However, PGZ causes weight gain, increases osteoporosis risk and bladder cancer, and deteriorates heart failure [9].

It's worth noting that the risk of cardiovascular (CVD) and kidney diseases increases in the patients with T2DM, which can develop liver- or multisystem diseases-related morbidity and mortality [13,14]. Hence, the researchers tried to find new antidiabetic agents being as effective as TZD with less side effects that concomitantly improve liver fibrosis and reverse the severity of NAFLD.

Recently, Empagliflozin (EMPA) as the newest antidiabetic agent with the mechanism of sodium-glucose co-transporter-2 inhibitor (SGLT2i) shows pleiotropic properties including cardiovascular and renal protective effects in patients with established cardiovascular or kidney diseases [15,16]. On the other hand, according to animal studies, EMPA shows anti-inflammatory and anti-oxidative properties, which may prevent the progression of NAFLD. According to a few human studies, EMPA ameliorated SLD and improved fibrosis in patients with diabetics and non-diabetics NAFLD [17], [18], [19].

Generally, regarding the superior properties of EMPA compared with PGZ, current study was designed to assess the efficacy of EMPA in comparison with pioglitazone in T2DM patients receiving metformin at least 1500 mg for three months.

Section snippets

Study design

This study was an open-label, randomized clinical trial study registered at the Iran Clinical Trials Registry, which can be accessed www. https://www.irct.ir/ ↗ (Registration number: IRCT20220928056051N1). The study conformed to the Helsinki Declaration [20] and followed all regulations relevant to human experimentation. Ethical approval was obtained

from ethics committee of UMSU (NO. IR.UMSU.REC.1401.180). The written informed consent was signed by all participants before entry to study. …

Participants and inclusion/exclusion criteria

…

Results

Of 278 patients that were evaluated for eligibility, sixty-six had inclusion criteria of the study and finally, sixty patients completed the study (EMPA group, n=30, and PGZ group, n=30) (Fig.1), from whom 25 patients were men (n=12 in PGZ group) and 35 were women (n=18 in PGZ group). The mean (±SD) age of participants in PGZ and EMPA groups were 53.33±7.24 years (range 41–71) and 51.83±7.96 years (range 37–65), respectively. No significant differences were observed in gender and age …

Discussion

Pioglitazone effectiveness had demonstrated in NAFLD and improving liver histology, but before considering to use, the risks and benefits of treatment should be evaluated. Pioglitazone does not have cardio protective properties, and concerns are running high about the association of PGZ with bladder cancer. Due to adverse effects following long-term use of PGZ in T2DM patient with NAFLD, investigation for substituting an appropriate pharmacological therapy with the least side effects and more …

Limitations

This study had some limitations as follows: It is better to considered patients with the higher stage of liver fibrosis (stage ≥2) as a population of study, due to necessity of receiving medication therapy in company with healthy dietary and physical activity. Besides, we did not evaluate the compliance of our participants to dietary and physical activity prescriptions during the study which may potentially confound the results. …

Conclusion

This study demonstrated that combination of EMPA with metformin did not inferior to combination of PGZ with metformin and both ameliorated SLD. The superiority of EMPA to

PGZ was a remarkable reduction in body weight and BMI, which is a keystone to improve NAFLD. In addition, patients receiving EMPA had experienced more changes in WC compared to PGZ. Finally, it is recommended to conduct the multi-center studies with larger sample size to confirm the results. …

Ethics approval and statement

From Urmia University of Medical Sciences (NO. IR.UMSU.REC.1401.180). …

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CRediT authorship contribution statement

Laya Hooshmand Gharabagh: Writing – original draft. **Ali Shargh:** Methodology, Investigation. **Mohammad Reza Mohammad Hosseini Azar:** Formal analysis, Data curation, Conceptualization. **Ayda Esmaeili:** Supervision. …

Declaration of competing interest

The authors declared that no competing of interest are existed. …

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