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.

Effects of Combination Therapy with Empagliflozin and Metformin on Interleukin-1β and Interleukin-6 Secretion in Type 2 Diabetes Patients

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ABSTRACT

Type 2 diabetes (T2D) is defined by persistent inflammatory processes. This study evaluated the anti-inflammatory properties of empagliflozin in combination with metformin therapy in patients with T2D.

In this prospective cohort study, 50 individuals with type 2 diabetes were non-randomly assigned to receive metformin (MTF, n=25) or empagliflozin (10 mg/day) and metformin (EMPA+MTF, n=25) and followed for 6 months. Fasting blood glucose (FPG), HbA1c, body mass index (BMI), glomerular filtration rate (GFR), and urinary albumin were measured at baseline and then 6 months later. Interleukin-1beta (IL-1β) and interleukin-6 (IL-6) secretion from isolated and stimulated peripheral blood mononuclear cells were measured using ELISA and compared in the different study groups.

The MTF+EMPA group showed significantly decreased levels of FPG, HbA1C, and body mass index compared to the baseline. FPG and HbA1c in the MTF+EMPA group showed a significant decrease six months after treatment versus the MTF group. A significant reduction in IL-1β levels was observed at the six months post-treatment compared to baseline and in relation to the MTF group after six months. The levels of IL-6 exhibited no significant differences, both within and between the study groups. Significant direct correlations were observed between IL-1β levels and FPG as well as HbA1c within the MTF+EMPA group following six months of treatment.

Incorporating empagliflozin (10 mg/day) into metformin treatment markedly enhanced glycemic regulation and lowered IL-1β secretions, indicating a possible anti-inflammatory benefit in overweight individuals with T2D following six months of treatment.

Keywords: Empagliflozin; Interleukin-1Beta; Interleukin-6; Metformin; Type 2 diabetes

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INTRODUCTION

Diabetes constitutes a pervasive global health issue that poses a significant challenge to health authorities

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across the globe. The escalating incidence of this chronic ailment accentuates the imperative for extensive research directed toward formulating innovative and efficacious strategies for managing and mitigating its ramifications.[1,2] A principal mechanism underlying diabetes is insulin resistance. Numerous studies have demonstrated a correlation between inflammatory processes instigated by immune factors, such as interleukins, tumor necrosis factor, and adipokines, and the insulin resistance associated with diabetes.[3]

Diabetes is increasingly recognized as a systemic disease not only characterized by insulin resistance but also closely associated with chronic inflammation. In particular, inflammation within adipose tissue contributes to the progression of insulin resistance by elevating levels of proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), Interleukin-(IL)-1 and interleukin-6 (IL-6) .[4,5] These cytokines play a key role in perpetuating a state of systemic low-grade inflammation, exacerbating insulin resistance, and contributing to the broader metabolic disorders observed in type 2 diabetes (T2D). This inflammatory process highlights the complexity of diabetes pathophysiology, in which metabolism and immune responses are closely related.[4,5]

Managing chronic hyperglycemia is an intricate and challenging process that is influenced by numerous physiological factors, lifestyle choices, and the level of patient adherence.[6] In our study, key gaps in existing knowledge regarding diabetes management were considered by examining the underlying mechanisms of current therapy. Although significant progress has been madein treatment diabetes treatment, particularly using drugs such as metformin and empagliflozin,[7,8] there is limited understanding of how these drugs interact with mediators of inflammation, particularly proinflammatory cytokines (e.g., IL-1β and IL-6), and how they modulate the glucose levels and inflammation. Understanding these pathways may lead to more specific and effective interventions, improving overall diabetes management.[9]

Accordingly, researchers are investigating innovative medications such as empagliflozin and metformin to understand their effects on hyperglycemia and modulation of IL-1 and IL-6 levels. Studies indicate that empagliflozin shows promise in reducing IL-1 secretion and controlling hyperglycemia; however, it does not significantly affect IL-6 levels.[10,11] Several studies also show that the efficacy of empagliflozin may be associated with its ability to regulate IL-1. This suggests that it may clearly affect the cytokine profile compared with other diabetes treatments.[12–14]

Therefore, it is essential to investigate whether combining empagliflozin and metformin improves hyperglycemia control and reduces inflammatory cytokines secretion. This study aims to investigate IL-1β and IL-6 secretion to improve understanding of the mechanisms of action of empagliflozin and metformin on IL-1β and IL-6 secretion in patients with T2D. By further exploring the possible anti-inflammatory properties of these medications at particular cytokine concentrations, it becomes possible to create more focused and efficient approaches for controlling T2D.

MATERIALS AND METHODS

Study Design

This prospective cohort study was conducted in a diabetes clinic at Shahid Beheshti University Hospital in Hamadan, Iran, among patients with T2D who received metformin, during the period from March to December in the year 2023.

Participants

The study population consisted of 50 T2D who were receiving metformin (made of Iran) at a dose of1000–1500 mg/day. All participants provided informed consent following approval by our Institute Research Ethics Committee (IR.UMSHA.REC.1399.777). Body mass index (BMI) was recorded for each participant. Convenience and sequential sampling were used to recruit the participants in this prospective cohort study. Participants were divided into case (n=25, comprising 10 males and 15 females) and control groups (n=25, consisting of 8 males and 17 females) through a non-randomized approach, utilizing an unblinded design. The case group received 10 mg/day of empagliflozin (made of Iran) added to their existing metformin therapy (EMPA+MTF group), whereas the control group maintained their standard treatment protocol, receiving the same metformin dose without any supplementary medication (designated as the MTF group). In addition, glomerular filtration rate (GFR)was assessed at 1 month, 3 months, and 6 months after initiation of the treatment.

Inclusion criteria were diagnosis of T2D based on the ADA 2022 criteria, age between 40 and 60 years, a GFR greater than 60 mL/min, a BMI between 25 and 30

kg/m², and an HbA1c level greater than 7.5% but less than 9%. The exclusion criteria were HbA1c≥9%, macroalbuminuria, recent infections or antibiotic use, organ failure, malignancy, autoimmune diseases, cardiovascular disease, and alcohol or tobacco use.

Samples Collection and In Vitro Assessments

Peripheral blood samples were collected in EDTA tubes at baseline and after six months of combination and monotherapy. Fresh peripheral blood mononuclear cells (PBMCs) were isolated using Ficoll-Hypaque (Histopaque-1077, Sigma, Germany) density gradient centrifugation at 2200 rpm for 25 minutes. The PBMCs were then collected and washed three times with sterile phosphate-buffered saline (PBS). Cell viability was confirmed using trypan blue staining. In the next step, fresh PBMCs (2×10^5 cells/well) were cultured in RPMI-1640 media containing 15% FCS in the presence of penicillin (50 U/mL)/Streptomycin (50 µg) and stimulated with anti-CD3 monoclonal antibody (2 µL/mL, Biolegend, USA) for four days. After 4 days of stimulation, the supernatants were collected and stored at -80 °C until cytokine measurements. IL-1β and IL-6 levels in the supernatants were then measured using commercial ELISA kits (PishtazTeb, Tehran, Iran) as per the manufacturer's instructions. Laboratory evaluations including fasting plasma glucose (FPG), hemoglobin A1c (HbA1c), serum creatinine, lipid profile, and GFR were conducted at the certified diagnostic laboratory within the university hospital, following standard protocols.

Statistical Analysis

Independent t-tests were used to analyze between-group differences, and within-group changes were evaluated using paired t-tests. All quantitative data were presented as mean ± SD. Correlations were assesed using Pearson's coefficient analysis. A p value of <0.05 was considered statistically significant. All statistical analyses were performed by SPSS ver. 21 (SPSS Inc., Chicago, IL, USA).

RESULTS

In this prospective cohort, two groups of age- and sex-matched T2D patients received either 1000–1500 mg/day of metformin (MTF group) or a combination of 1000–1500 mg/day of metformin plus 10 mg/day of empagliflozin (MTF+EMPA group) over a follow-up period of 6 months. All participants completed the study, and no adverse effects were noted. Laboratory characteristics were also similar in the two groups at baseline (p>0.05).

The clinical and laboratory characteristics of the MTF group remained stable from baseline to six months later. In contrast, the MTF+EMPA group experienced significant reductions in FPG, HbA1c, and BMI from baseline (p<0.0001, p<0.0001, and p=0.017, respectively).

In between-group analysis, only FPG and HbA1c in the MTF+EMPA group showed a significant decrease at 6 months after treatment (p=0.002 and p=0.03, respectively) (Table 1).

Cytokine Assessments

The mean levels of secreted IL-1β and IL-6 in the supernatants of stimulated PBMCs were compared between the two patient groups. Results showed a significant decrease in IL-1β levels in the MTF+EMPA group at six months post-treatment compared to baseline (259.4 ± 133.3 vs. 153.1 ± 106.4 pg/mL, p=0.007). Additionally, a significant reduction in IL-1 β levels was observed in the MTF+EMPA group compared with the MTF group after 6 months (275.6 ± 251.8 vs. 153.1 ± 106.4 pg/mL, p=0.03) (Figure 1).

No significant differences were found for IL-6 levels within or between the two patient groups (117.2 ± 87.8 at baseline vs. 112.4 ± 89.3 pg/mL after 6 months in the MTF+EMPA group, p>0.05; and versus 118.8 ± 78.09 pg/mL in the MTF group after 6 months, p>0.05, Figure 2).

At baseline, there were no significant associations between IL-1β or IL-6 levels and FPG or HbA1c contents in either group (p>0.05), as shown by Pearson correlation analyses. However, after 6 months, a significant direct correlation was observed in the MTF+EMPA grou between IL-1β levels and FPG (r=0.46, *p=0.019*) and HbA1c (r=0.54, p=0.005) p (Table 2).

Table 1. Comparisons of the main characteristics and laboratory findings between the two groups of patients at the baseline and 6 months after treatment

Variables	Metformin (MTF) group (N=25)		p^a	Metformin and empagliflozin (MTF+EMPA) group (N=25)		p^b	p^c
	Baseline	After 6 months		Baseline	After 6 months		
Gender (male/female)	25 (8 / 17)	-	-	25 (10 / 15)	-	-	-
Age, years	51.3 ± 7.64	-	-	54.7 ± 5.94	-	-	-
FPG, mg/dL	164.7 ± 38.07	153.8 ± 32.8	0.19	169.4 ± 39.6	127.6 ± 21.54	<0.0001	0.002
HbA1c, %	7.50 ± 0.89	7.28 ± 0.82	0.31	7.81 ± 0.81	6.81 ± 0.67	<0.0001	0.03
BMI, kg/m²	27.73 ± 3.69	27.97 ± 3.87	0.56	28.13 ± 4.32	25.33 ± 3.99	0.017	0.56
GFR, mL/min/1.73m²	77.69 ± 15.02	79.18 ± 11.64	0.62	75.72 ± 16.69	75.99 ± 6.37	0.93	0.33
Serum creatinine, mg/dL	0.91 ± 0.17	0.88 ± 0.18	0.49	0.95 ± 0.34	0.96 ± 0.18	0.80	0.12
Albuminuria, mg/dL	16.85 ± 7.40	15.2 ± 5.40	0.27	17.37 ± 8.46	18.51 ± 8.69	0.51	0.09

All quantitative data are presented as mean ± SD. Comparisons between baseline and after sixth month in MTF group. Comparisons between baseline and after sixth month in MTF+EMPA group. Comparisons between two groups after sixth month. Abbreviations: BMI: body mass index; EMPA: empagliflozin; FPG: fasting plasma glucose; GFR: glomerular filtration rate; HbA1c: hemoglobin A1c; MTF: metformin; SD: standard deviation.

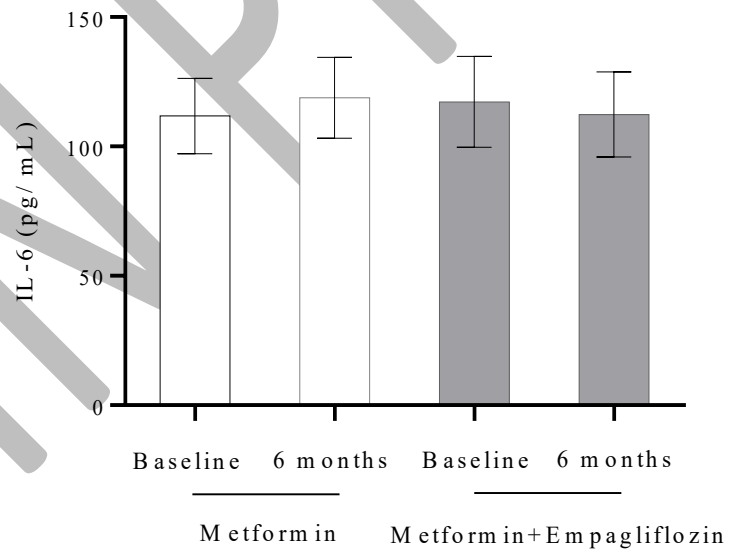

Figure 1. Comparison of the levels of IL-1β at baseline and 6 months after treatment in the MTF and MTF+EMPA groups.

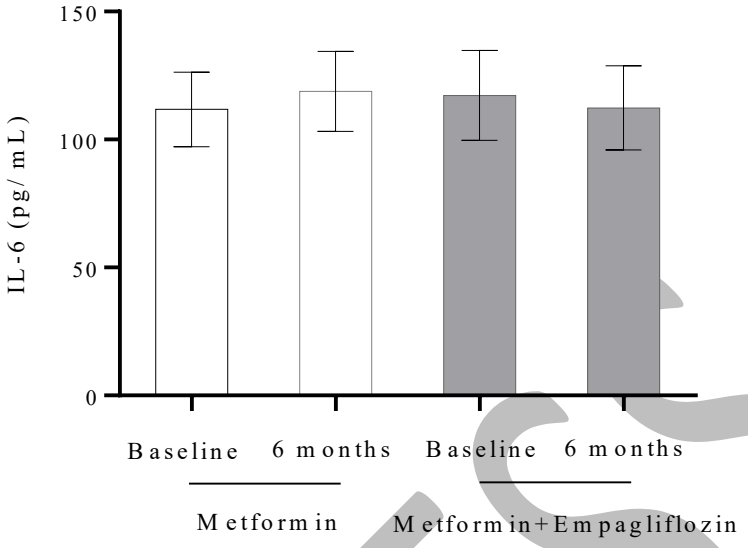

Figure 2. Comparison of the levels of IL-6 at baseline and 6 months after treatment in the MTF and MTF+EMPA groups.

Table 2. The correlation between IL-1β and IL-6 with FPG and HbA1c percentage in two study groups at the 6 months of treatment

Study group	Statistics	FPG	HbA1c
MTF group			
IL-1β	r	-0.09	-0.30
	p	0.64	0.88
IL-6	r	-0.11	0.16
	p	0.58	0.44
EMPA+MTF group			
IL-1β	r	0.46	0.54
	p	0.019	0.005
IL-6	r	0.18	0.07
	p	0.36	0.70

EMPA: empagliflozin; FPG: fasting plasma glucose; HbA1c: hemoglobin A1c; IL: interleukin; MTF: metformin.

DISCUSSION

The present study demonstrated that combination therapy with metformin and empagliflozin are more effective than metformin monotherapy in controlling blood glucose and HbA1c in patients with T2D. More importantly, this combination therapy was significantly correlated with decreased levels of IL-1β in the presence of controlled FPG and HbA1c levels in our T2D patients.

Empagliflozin has been shown to exert anti-inflammatory effects in addition to its glucose-lowering properties.[7,8] One study demonstrated that empagliflozin reduces levels of high-sensitivity C-reactive protein (hsCRP), a marker of systemic inflammation. This anti-inflammatory action may extend the therapeutic use of empagliflozin beyond glycemic control, particularly in nondiabetic conditions such as heart failure and chronic kidney disease. The beneficial effects of empagliflozin in these conditions may be partly be attributed to its

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ability to mitigate inflammation, highlighting its potential role in managing diseases associated with chronic inflammation.[15,16]

A meta-analysis of 15 randomized controlled trials (RCTs) involving 7891 individuals (5374 in the empagliflozin group and 2517 in the control group) demonstrated significant improvements in glycemic control, body weight, and blood pressure with empagliflozin as both monotherapy and add-on therapy in patients with type 2 diabetes mellitus (T2DM), compared to placebo.[7] Further support comes from a case-control study conducted by Moghimi et al where 50 patients were followed over 6 months, and the empagliflozin group demonstrated significant reductions in FPG and HbA1c levels compared to the control group, which did not receive empagliflozin.[8,17] Our findings are consistent with previous research that showed better glycemic control and reduced levels of the inflammatory cytokine IL-1β in T2DM patients treated with EMPA+MTF compared with those treated with MTF alone.

Empagliflozin may also regulate the immune system. Our previous study in patients with T2D receiving empagliflozin for 6 months demonstrated reduced (T helper 17 cell) T_H17-related inflammatory markers and increased Treg cell markers, indicating the anti-inflammatory effects of this therapeutic intervention. It also depicted a decreased T-helper cell proliferation and shifted the immune response towards a more regulatory profile in the empagliflozin group compared to the control T2D patients.[8] Consistently, the present study on T2D patients further supports the anti-inflammatory properties of empagliflozin, as shown by lower levels of IL-1β in this group of T2D patients. Although, the observation of insignificant differences in IL-6 levels among the study groups highlighted the need for caution in interpreting the findings.

Khan et al demonstrated in animal models that empagliflozin nanoparticles reduced inflammatory mediators and oxidative stress in diabetic mice.[18] Our study results support the anti-inflammatory properties of empagliflozin in reducing IL-1β production in PBMCs from T2D patients. Canet et al conducted a study with 16 T2D patients who were given 10 mg/day of empagliflozin in addition to standard care for 16 weeks. They noted reductions in body weight, BMI, and HbA1c over a period of 12 to 24 weeks, as well as significant decreases in IL-6 expression.[19] Our 24-week cohort study found no significant differences in IL-6 levels between patients taking EMPA+MTF and the group taking only MTF. However, the EMPA+MTF group had lower levels of FPG, HbA1c, and BMI, which aligns with previous studies. Also, in the research conducted by Jigheh et al, examining the impact of empagliflozin on renal inflammation and oxidative stress in streptozotocin-induced diabetic murine models, administration of empagliflozin at a dosage of 10 mg over a duration of 4 weeks demonstrated a significant reduction in renal inflammation, along with a decrease in renal expression of inflammatory cytokines, including TNF-α, and a concomitant reduction in urinary secretion of IL-6.[20] The findings of the current investigation align with the results reported by Jigheh et al regarding the influence of empagliflozin on IL-1β levels.

In a separate investigation by Iannantuoni et al assessing the ramifications of daily administration of 10 mg of empagliflozin on the inflammatory profile and leukocyte antioxidant response in a cohort of 15 individuals with T2D, it was observed that the expression of glutathione reductase and catalase in leukocytes, as well as serum levels of IL-10, exhibited an increase following 24 weeks of empagliflozin therapy. They indicated that empagliflozin possesses both antioxidant and anti-inflammatory attributes that may prove advantageous in mitigating cardiovascular incidents among diabetic patients.[21]

In a comparative study conducted by Tan et al, which evaluated the effects of canagliflozin and empagliflozin on levels of interferon-γ (IFN-γ), TNF-α, and IL-6 in diabetic subjects as well as associated cardiovascular events in a sample of 32 men diagnosed with diabetes, the study's outcomes revealed a reduction in

IFN-γ, TNF-α, and IL-6 among patients treated with empagliflozin, which correlated with a diminished risk of cardiovascular events; however, canagliflozin exhibited a more pronounced effect in lowering hemoglobin A1C levels.[22] Consistent with these results, we noted markedly reduced concentrations of IL-1β within the EMPA+MTF cohort of individuals with T2D. Interestingly, the lack of significant variations in IL-6 levels across our study groups may be attributed to the sample size and the clinical characteristics of the patients involved. This observation arises from our decision to exclude patients diagnosed with cardiovascular disease from the research.

In the present study, among the groups treated with metformin and empagliflozin, a significant and direct correlation was observed between the reduced levels of

IL-1β and the lower concentrations of FPG as well as the percentage of HbA1c. The variation in IL-6 concentrations may result from differences in sample sizes, patient characteristics, and the medications taken by individuals with T2D across the various studies. It is crucial to acknowledge limitations, including a limited sample size, a short follow-up duration, the study's unblinded design, non-random patient assignments, and the insufficient diversity in antidiabetic treatment plans. Further investigations are needed to explore these inconsistencies and their effects on inflammatory results.

Overall, this study provides additional evidence supporting the efficacy of empagliflozin in improving blood glucose control and reducing inflammatory markers in patients with T2D. Our findings align with previous reports, underscoring the potential anti-inflammatory benefits of empagliflozin in T2D patients. However, future studies with larger cohorts and longer follow-up periods are warranted to strengthen the reliability and generalizability of these results. Furthermore, additional research is necessary to further clarify empagliflozin's anti-inflammatory effects on various cytokine profiles, which may reveal broader implications for its use beyond glycemic control.

In conclusion, adding 10 mg of empagliflozin to metformin treatment for T2D patients could enhance glycemic control and lower inflammation. This is supported by reductions in FPG, HbA1c, and IL-1β levels after six months of treatment. However, there were no notable changes in IL-6 levels. While these results suggest potential advantages for clinical practice, additional research is needed to validate the sustained effectiveness and safety of this combination therapy.

STATEMENT OF ETHICS

This prospective cohort was conducted after approval by the ethics committee of Hamadan University of Medical Sciences (IR.UMSHA.REC.1399.777) and adhered to the principles outlined in the Declaration of Helsinki.

FUNDING

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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DATA AVAILABILITY

Data are available upon reasonable request by contacting the corresponding author.

AI ASSISTANCE DISCLOSURE

Not applicable.

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