Randomized study of the effects of Empagliflozin and Topiramate dual therapy on anthropometric and metabolic indices in non-diabetic individuals with overweight/obesity on a calorie-restricted diet

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Research Article

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Abstract

Objectives: The objective of this study was to evaluate the effectiveness of the combined use of empagliflozin (EMPA) and topiramate (TPM) versus a placebo in overweight/obese individuals without diabetes on a calorie-restricted diet.

Methods: In this study, 44 non-diabetic and overweight/obese subjects who were on a calorie restricted diet were randomly assigned into 2 groups: 1) Participants received a 10 mg EMPA tablet daily plus TPM tablet (at the first week 25 mg once a day and from the second week 25 mg twice a day); 2) Participants received an empagliflozin placebo (daily) plus a topiramate placebo (as mentioned for topiramate tablet in group 1), for 12 weeks. At baseline and weeks 4, 8, 12, weight, height, body mass index (BMI), waist circumference (WC), and body composition were evaluated. Before and after the intervention, blood pressure, C reactive protein, and glucose and lipid profile parameters were measured.

Results: The EMPA/TOP group, compared to placebo, had a greater percent change of weight at week 12 (-8.92 ± 1.80 vs. -4.93 ± 1.17). The intervention group had a greater percent change of fat mass and fat percent at week 12 ($P<0.05$). However, there was no difference in the percent of change in fat-free percent between the two groups at week 12 ($P=0.577$). Within-group analysis found a significant reduction in SBP, DBP, FBS, insulin, HOMA-IR, TC, LDL, HDL, TG, and CRP in both groups ($P<0.05$). The Time × Group effect was significant only for DBP ($P=0.034$). At week 12, no statistically significant difference was observed between the two groups in any of mentioned variables ($P>0.05$).

Conclusion: In non-diabetic overweight/obese individuals, the combination of EMPA/TPM and calorie restriction led to a notable decrease in body weight and was generally well-tolerated. Further research is required to evaluate the potential advantages of utilizing this combination for sustained weight management in the long run.

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- Trial registration number: IRCT20230114057122N1
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1. Introduction

Around 39% and 13% of adults globally are classified as overweight and obese, respectively (1). These conditions have been linked with significant health concerns such as cardiovascular disease, type 2 diabetes (T2D), non-alcoholic fatty liver disease, musculoskeletal disorders, and certain forms of cancer (1, 2). As a result, those who are affected may experience a notable impact on their overall quality of life, and the broader society may also encounter consequences such as an upsurge in healthcare expenses. On the other hand, losing excess weight in overweight and obese individuals can help alleviate their cardiometabolic risks (3).

The prevalence of obesity has risen significantly due to advancements in technology, sedentary lifestyles, and increased availability of high-calorie foods (4). The significance of genetic factors in this context cannot be overlooked. It thus appears that obesity can be treated in a multifactorial manner, including lifestyle modification, behavioral therapy, medication, and bariatric surgery. The primary treatment for obesity and being overweight is typically centered on lifestyle adjustments, including reducing energy intake and increasing physical activity. Studies and guidelines from the Endocrine Society suggest that pharmacotherapy may be a suitable supplement to lifestyle modifications for individuals with a body mass index (BMI) of 30 or higher, or those with a BMI of 27–30 and at least one weight-related complication (5).

There is a growing effort to identify the most effective anti-obesity medications among the new generation of drugs. Factors such as weight loss potential, availability, cost, efficacy, and side effects are all being carefully considered in this pursuit. Despite the development of new, highly potent drugs, their cost and availability remain limiting factors. As a result, there are ongoing efforts to discover new drugs or drug combinations. In this regard, several glucose-lowering therapies have been found to result in weight loss, leading to a need for further investigation into their potential use in obese individuals who are at risk of developing diabetes. Sodium-glucose cotransporter 2 (SGLT2) inhibitors are particularly intriguing, as they promote weight loss by increasing urinary glucose excretion, leading to mild diuresis and caloric loss. However, it's worth noting that these drugs can also increase appetite as a compensation mechanism (6, 7). Studies suggest that up to 11 kg of weight loss may occur as a result of the excretion of 400 kcal of energy in urine (8). However, it's important to note that this effect may be partially offset by a compensatory increase in food intake. Combining an SGLT2 inhibitor with a medication that decreases food intake could potentially be a more effective approach for overcoming physiological resistance to weight loss compared to using a single medication (9). The use of such combination pharmacotherapy may lead to greater weight loss outcomes than using a single medication alone. In this regard, it has been observed that weight loss has occurred in clinical trials of topiramate, a sulfamate-substituted monosaccharide that has been used in the treatment of seizure disorders (10). Weight loss has been observed in several rodent models of obesity that were treated with topiramate (11). Topiramate acts as an agonist of gamma-aminobutyric acid receptors, which leads to increased satiety and decreased appetite (5).

As such, combining the SGLT2 inhibitor empagliflozin with topiramate may be particularly effective for achieving sustained weight loss, as their mechanisms of action are distinct and potentially complementary. In this 12-week study, empagliflozin and topiramate were co-administered to overweight/obese individuals without diabetes to assess their efficacy and safety.

2. Methods and Materials

The current study was a randomized, double-blind, placebo- controlled clinical trial. Recruitment was conducted in the nutrition clinic at Shahid Beheshti University of Medical Sciences, Tehran, Iran. The protocol of this study was approved by the Medical Ethics Committee of Shahid Beheshti University of

Medical Sciences, is in conformity with the Declaration of Helsinki (approval number: IR.SBMU.RETECH.REC.1401.137) and was registered at the Iranian Registry of Clinical Trials (IRCT registration number: IRCT20230114057122N1) which is available at: https://www.irct.ir/trial/68026. All participants signed an informed consent form.

This study followed the CONSORT guidelines (12), and the details of the study are shown in Figure 1.

Participants were 44 non-diabetic individuals with overweight/obesity aged over 18 years. The inclusion criteria were consist of: BMI = 30-40 kg/m^2 or ≥ 27 kg/m^2 and < 30 kg/m^2 in the presence of controlled hypertension and/or dyslipidaemia (two months of stable medication must have passed before enrollment for those conditions); were not suffered from diabetes, thyroid, renal, and hepatic diseases; not breastfeeding or pregnancy; not taking laxative and/or anti-inflammatory medications. Exclusion criteria include recent alterations in weight; history of eating disorders; significant cardiovascular diseases; previous weight-loss surgery; uncontrolled hypertension; or psychiatric- or significant central nervous system (CNS)-associated disorders, and current long term use of psychotropic medications; the occurrence of any acute disease during the study; unwillingness to continue the study; and less than 90% compliance with the treatment.

2.1. Sample size

To estimate the sample size, we considered the significance level of 0.05, power of 0.80, standard deviation of 0.16, and assuming a 4% decrease in body weight as a significant change (13,14). This resulted in a requirement of 19 participants per group. Assuming 25% dropout rate, we recruited 23 participants for each group, totaling 46 individuals with excess weight.

2.2. Randomization and intervention

All participants consumed hypocaloric diets - 500 kcal under assumed energy requirements estimated using the Mifflin-Jeor St equation. Subjects were instructed not to change their usual physical activities. Participants were assigned to treatment groups using computer-generated random numbers. A random allocation of participants into two groups was conducted: 1) a 10 mg empagliflozin (daily) before breakfast, plus a topiramate tablet (25 mg/day before dinner in the first week of intervention and if tolerated by the participants, the dose was increased to 25 mg twice a day from the second week till end of the intervention); and 2) an empagliflozin placebo (daily) before breakfast, plus a topiramate placebo (as mentioned for topiramate tablet in group 1). In addition, topiramate must be taken within one hour of breakfast and dinner in order to maintain compliance.

Iranian companies Dr. Abidi and Araydaru supplied empagliflozin and topiramate tablets, respectively. The placebos for empagliflozin and topiramate contained maltodextrin, respectively, and were provided by “Roshd” Pharmaceutical Incubation Center of Tehran University of Medical Sciences, Tehran, Iran. There was no distinguishable difference between the placebos and empagliflozin and topiramate tablets in color, size, shape, packaging, smell or taste.

Counseling was given verbally and in writing on how to consume the tablets or placeboes. Counting pills every two weeks was used to evaluate compliance.

Using a random number table, the patients were randomly assigned to the empagliflozin and topiramate coadministration or the placebo group by someone who was not part of the study protocol. Topiramate, empagliflozin, and their placebo were placed in identical and unlabeled containers. These containers were labeled with patient numbers using a randomization list generated by the study leader. A blinded assignment process was used for all researchers and participants.

2.3. Outcome Measures

The participants were asked to fill out a questionnaire at the beginning of the intervention regarding their demographic information, medications, diseases, and probable supplement and/or medication use.

During 3 days (2 weekdays and 1 weekendday), dietary intake was monitored via 24-h food recalls, and energy intake was calculated via Nutritionist 4. The Persian version of the International Physical Activity Questionnaire (IPAQ) was utilized to evaluate physical activity level and it was reported in MET-min/week (15).

With individuals wearing light clothes, anthropometric measurements were obtained, including height, weight, body mass index (BMI), waist circumference (WC), and body composition and evaluated with validated measurement techniques at baseline, weeks 4, 8, and 12. We measured height using a stadimeter while people stood without shoes, and rounded the measurements to the nearest centimeter (cm). Body weight was evaluated to the nearest 0.1 kg (Beurer, Germany) while the individuals were minimally clothed and without shoes. BMI was calculated as weight divided by height squared and expressed in kg/m^2. The WC value was measured with an inflexible measuring tape from the highest point of the iliac crest to the lowest rib in the mid-axillary line and is given in centimeters. Body composition data including body fat mass (FM), fat free mass (FFM), and the percentage of FM and FFM were obtained by Bioelectrical Impedance Analyzer (Quad scan 4000; Bodystat).

Blood pressure was measured at baseline and week 12 after sitting for at least 10 min of rest.. Measurements were taken with a digital sphygmomanometer (Omron M2 Basic, UK). The mean of three measurements was taken for each measurement of systolic (SBP) and diastolic blood pressure (DBP) (mmHg).

We collected blood samples, after 12-hour overnight fasting, before and after the intervention, and serum samples were separated by centrifugation at 800-1000 RPM for 10 minutes; the serum samples were then frozen and kept at $-80^{o}C$ for biochemical analysis.

Before and after the intervention, fasting blood glucose, insulin, glycosylated hemoglobin (HbA1c) (measured in whole blood), total cholesterol (TC), HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C), TG, and C-reactive protein (CRP) were measured.

Lipid profiles were assessed using enzyme methods (Pars Azmoon Co., Tehran, Iran); inter-and intra-assay coefficient of variations (CV) were less than 1.6%. By using an auto-analyzer (SELECTRA-E) the levels of FBG (Pars Azmoon Co., Tehran, Iran) and HbA1C (Pishtazteb Co., Tehran, Iran), were evaluated with enzymatic methods; inter-and intra-assay coefficient of variations (CV) were less than 2.2%. Fasting serum insulin was measured by the electrochemiluminescence immunoasaay, using Roche Diagnostics kits and the Roche/Hitachi Cobas analyzer (GmbH, Mannheim, Germany); intra- and inter-assay coefficients of variation were 1.2 and 3.4 %, respectively.

Insulin resistance were assessed by HOMA-IR (16), as follows:

Insulin resistance (HOMA-IR) = [FBG (mg/dl) x Fasting insulin (μIU/ml)]/ 405

Serum CRP levels (Biorex Fars Co., Tehran, Iran) were assessed by an imonotorbidometric method using a SELECTRA-E autoanalyzer.

2.4. Statistical Analysis

All statistical analyses were performed with SPSS (Version 22.0; SPSS Inc., Chicago, IL). The normal distribution of the variables was examined and confirmed using the Kolmogorov-Smirnov test. All results were presented as mean ± SD. Categorical variables were demonstrated as frequencies and percentages. Chi-square test was used to assess the differences between categorical variable. The baseline differences of mean values were tested using independent sample t-test for continuous variables and Chi-square for categorical variables. A mixed between within ANOVA, also known as a split-plot ANOVA, was used to test for differences between two independent groups whilst subjecting participants to repeated measures. The mean values were compared within groups after the intervention using paired sample t-tests. $P < 0.05$ was considered statistically significant.

3. Results

3.1. General characteristics

Of 46 subjects firstly included in the study, one participant in each of the groups withdrew because of non-adherence of the intervention. Totally, 44 participants (16 males and 28 females) with overweight/obesity were randomly assigned to empagliflozin/topiramate (EMPA/TOP) or placebo groups. Sixteen participants (36%) were male. The baseline characteristics of study participants are provided in Table 1. The baseline mean body weight was 90.50 kg and the mean BMI was 33.67 kg/m^2 at the start of the study. There was no significant difference in sex, age, height, weight, BMI, WC, and physical activity between the two groups at the baseline ($P > 0.05$). Also, no significant change was observed in physical activity over time in any groups ($P > 0.05$).

Table 1
General characteristics of participants

Variable		Total (n = 44)	EMPA/TOP (n = 22)	Placebo (n = 22)	P†
Sex, n (%)					
Male		16 (36.4)	9 (40.9)	7 (31.8)	0.754
Female		28 (63.6)	13 (59.1)	15 (68.2)	
Age (years)		33.68 (10.30)	35.63 (11.84)	31.72 (8.31)	0.212
Height (cm)		163.79 (7.34)	164.22 (7.15)	163.36 (7.66)	0.701
Weight (kg)		90.50 (12.77)	90.81 (15.30)	90.18 (9.99)	0.872
BMI (kg/m^2)		33.67 (3.60)	33.54 (4.17)	33.79 (3.02)	0.821
WC (cm)		98.32 (2.11)	98.77 (1.71)	97.87 (2.40)	0.160
PA (MET/day)	Baseline	517.12 (71.96)	525.07 (77.02)	509.16 (67.36)	0.470
	Week 4	517.11 ± 70.29	524.77 ± 75.87	509.45 ± 65.08	0.476
	Week 8	517.47 ± 70.33	526.71 ± 77.44	508.22 ± 62.87	0.390
	Week 12	520.45 ± 63.42	528.82 ± 66.53	512.09 ± 60.52	0.388
	P¥	0.677	0.819	0.615	

3.2. Anthropometric indices and body composition

The mean of weight, BMI, WC, fat mass, fat-free mass, fat mass percentage, fat-free mass percentage, and fat mass to fat-free mass ratio at baseline, week 4, week 8, and week 12 was provided in Table 2. It was found that in both groups with a hypocaloric diet, there was a significant reduction in weight, BMI, WC, fat mass, fat percentage, fat-free mass, fat-free mass percentage, and fat mass to fat-free mass ratio over time ($P < 0.001$). In between-group comparison, the placebo group had a higher fat-free mass compared to the EMPA/TPM group at weeks 4 ($P = 0.014$), 8 ($P = 0.001$), and 12 ($P < 0.001$). No difference was observed between the 2 groups for any other variables at any other time point ($P > 0.05$). However, it was observed that the EMPA/TPM group had a greater decrease in weight (at weeks 8 and 12), BMI (at weeks 8 and 12), WC (at weeks 4), fat mass (at weeks 8 and 12), fat percent (at weeks 4 and 12), fat-free mass (at weeks 4, 8, and 12), fat-free percent (at weeks 4 and 12), and fat mass to fat-free mass ratio (at weeks 4, 8, and 12). Moreover, mixed between within ANOVA showed a significant Time × Group association for the weight ($P < 0.001$), BMI ($P < 0.001$), fat mass ($P < 0.001$), fat percent ($P < 0.001$), fat-free mass ($P < 0.001$), fat-free percent ($P = 0.001$), and fat mass to fat-free mass ratio ($P < 0.001$). Nevertheless, the Time × Group association was not statistically significant for WC ($P = 0.065$).

Table 2
Comparison of anthropometric measures and body composition between intervention and placebo groups during the study.

		Week 0	Week 4	Week 8	Week 12	P week 0–4†	P week 4–8†	P week 8–12†	P week 0–12¥
Weight (kg)	EMPA/TOP	90.81 ± 15.30	88.69 ± 14.92	86.43 ± 14.69	82.82 ± 14.80	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**
	Placebo	90.18 ± 9.99	88.33 ± 9.92	87.04 ± 9.87	85.75 ± 9.77	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**
	P Between groups††	0.872	0.927	0.873	0.443	0.114	**< 0.001**	**< 0.001**	**< 0.001¥¥**
BMI ($kg/m^{2)}$	EMPA/TOP	33.54 ± 4.17	32.76 ± 4.11	31.92 ± 4.05	30.58 ± 4.10	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**
	Placebo	33.79 ± 3.02	33.10 ± 3.00	32.61 ± .95	32.13 ± 2.89	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**
	P Between groups††	0.821	0.758	0.524	0.156	0.114	**< 0.001**	**< 0.001**	**< 0.001¥¥**
WC (cm)	EMPA/TOP	98.77 ± 1.71	98.70 ± 1.71	97.64 ± 1.71	96.66 ± 1.83	**0.007**	**< 0.001**	**< 0.001**	**< 0.001**
	Placebo	97.87 ± 2.40	97.67 ± 2.50	96.75 ± 2.63	95.91 ± 2.54	**0.001**	**< 0.001**	**< 0.001**	**< 0.001**
	P Between groups††	0.160	0.117	0.195	0.265	**0.022**	0.277	0.435	0.065¥¥
Fat mass (kg)	EMPA/TOP	34.42 ± 2.79	34.19 ± 2.99	32.36 ± 2.95	29.34 ± 3.02	**0.001**	**< 0.001**	**< 0.001**	**< 0.001**
	Placebo	33.29 ± 2.77	32.92 ± 2.80	32.21 ± 2.81	30.91 ± 2.81	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**
	P Between groups††	0.184	0.150	0.864	0.081	0.146	**< 0.001**	**< 0.001**	**< 0.001¥¥**
Fat Percent (%)	EMPA/TOP	38.94 ± 7.25	39.60 ± 7.50	38.53 ± 7.62	36.57 ± 7.69	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**
	Placebo	37.33 ± 5.26	37.70 ± 5.38	37.44 ± 5.39	36.45 ± 5.17	**< 0.001**	0.074	**< 0.001**	**< 0.001**

		Week 0	Week 4	Week 8	Week 12	P week 0–4†	P week 4–8†	P week 8–12†	P week 0–12¥
	P Between groups††	0.406	0.339	0.588	0.951	**0.022**	**0.002**	**0.017**	**< 0.001¥¥**
Fat-Free Mass (kg)	EMPA/TOP	65.57 ± 2.79	63.82 ± 2.57	62.25 ± 2.58	60.35 ± 2.56	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**
	Placebo	66.70 ± 2.77	65.96 ± 2.96	65.25 ± 3.22	64.4 ± 3.22	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**
	P Between groups††	0.184	**0.014**	**0.001**	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001¥¥**
Fat-Free Percent (%)	EMPA/TOP	74.03 ± 12.12	73.79 ± 12.06	73.94 ± 12.50	75.00 ± 13.12	0.145	0.445	**0.014**	0.090
	Placebo	74.78 ± 8.36	75.50 ± 8.48	75.82 ± 8.73	75.97 ± 8.92	**< 0.001**	0.107	0.274	**0.003**
	P Between groups††	0.813	0.589	0.565	0.776	**< 0.001**	0.522	**0.037**	**0.001¥¥**
Fat Mass to Fat-Free Mass ratio	EMPA/TOP	0.52 ± 0.06	0.53 ± 0.06	0.52 ± 0.07	0.48 ± 0.07	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**
	Placebo	0.50 ± 0.06	0.50 ± 0.06	0.49 ± 0.07	0.48 ± 0.07	0.864	**0.001**	**< 0.001**	**< 0.001**
	P Between groups††	0.178	0.072	0.209	0.787	**< 0.001**	**0.001**	**< 0.001**	**< 0.001¥¥**

At the end of week 12, weight loss ≥ 5% of baseline weight was achieved by 100% of subjects receiving EMPA/TPM vs 36.4% (n = 8) in the placebo arm (P < 0.001) (Fig. 2A); weight loss ≥ 10% was observed by 31.8% (n = 7) vs 0.0%, respectively (P < 0.01) (Fig. 2B). Figure 3 shows the percent change in weight (A), BMI (B), and waist circumference (C). The EMPA/TPM group had a greater percent change of weight at weeks 8 (-4.84 ± 1.02 vs. -3.50 ± 0.96) and 12 (-8.92 ± 1.80 vs. -4.93 ± 1.17). Also, participants in the EMPA/TPM group had a greater percent change of BMI at weeks 8 (-4.84 ± 1.02 vs. -3.49 ± 0.97) and 12 (-8.92 ± 1.83 vs. -4.92 ± 1.18). The percent change of WC was significantly different between the two groups only in week 4 (P = 0.022).

As shown in Fig. 4, the EMPA/TPM group had a greater percent change of fat mass (A) and fat percent (B) at weeks 8 and 12 (P < 0.05). Moreover, a greater percent reduction was observed in the fat-free mass

of the EMPA/TPM group at weeks 4, 8, and 12 (Fig. 4C). However, there was no difference in the percent of change in fat-free percent between the two groups at week 12 (P = 0.577; Fig. 4D).

3.3. Metabolic markers

Table 3 compared the mean of metabolic indices at baseline and end of the study (week 12) between the EMPA/TPM and placebo groups. At the baseline, there was no significant difference in SBP, FBS, insulin, HOMA-IR, TC, LDL, HDL, TG, and hs-CRP between the two groups (P > 0.05). However, the placebo group had a lower level of DBP compared to the EMPA/TPM group at the start of the study (P = 0.036). At week 12, no statistically significant difference was observed between the two groups in any of mentioned variables (P > 0.05). Within-group analysis found a significant reduction in SBP, DBP, FBS, insulin, HOMA-IR, TC, LDL, HDL, TG, and CRP in both groups (P < 0.05). The Time × Group effect was significant only for DBP (P = 0.034).

Table 3
Comparison of metabolic indices between intervention and placebo groups during the study.

		EMPA/TOP	Placebo	P-value†	P-value¥
SBP (mmHg)	Baseline	13.53 ± 1.02	13.08 ± 1.08	0.164	0.498
	Week 12	12.54 ± 0.53	12.25 ± 0.41	0.054	
	P-value††	< 0.001	< 0.001		
DBP (mmHg)	Baseline	8.64 ± 0.57	8.30 ± 0.45	**0.036**	**0.034**
	Week 12	8.12 ± 0.21	8.05 ± 0.13	0.246	
	P-value††	< 0.001	0.004		
FBS (mg/dl)	Baseline	85.81 ± 7.68	83.44 ± 7.94	0.320	0.418
	Week 12	83.84 ± 6.78	81.80 ± 7.46	0.349	
	P-value††	< 0.001	< 0.001		
Insulin (µIU/ml)	Baseline	8.48 ± 2.95	8.15 ± 3.83	0.749	0.187
	Week 12	8.04 ± 2.68	7.85 ± 3.57	0.850	
	P-value††	< 0.001	< 0.001		
HOMA-IR	Baseline	1.79 ± 0.64	1.67 ± 0.78	0.607	0.147
	Week 12	1.66 ± 0.56	1.58 ± 0.72	0.711	
	P-value††	< 0.001	< 0.001		
TC (mg/dl)	Baseline	186.50 ± 27.23	191.03 ± 20.83	0.539	0.459
	Week 12	174.41 ± 23.77	180.03 ± 19.45	0.396	
	P-value††	< 0.001	< 0.001		
LDL (mg/dl)	Baseline	144.54 ± 17.03	137.75 ± 17.07	0.194	0.155
	Week 12	136.79 ± 15.74	131.61 ± 14.26	0.260	
	P-value††	< 0.001	< 0.001		
HDL (mg/dl)	Baseline	41.80 ± 3.17	41.60 ± 3.25	0.834	0.797
	Week 12	42.18 ± 3.19	42.02 ± 3.13	0.872	
	P-value††	0.022	0.002		
TG (mg/dl)	Baseline	154.25 ± 23.61	150.71 ± 19.70	0.593	0.124

		EMPA/TOP	Placebo	P-value†	P-value¥
	Week 12	147.73 ± 20.22	146.29 ± 18.39	0.807	
	P-value††	< 0.001	< 0.001		
CRP (mg/L)	Baseline	1.67 ± 0.45	1.53 ± 0.37	0.283	0.709
	Week 12	1.56 ± 0.46	1.44 ± 0.38	0.345	
	P-value††	0.001	0.002		

3.4. Adverse events

All adverse events observed during the trial were classified as mild. One participant in the intervention group experienced dysuria, while two others reported dizziness and headaches. None of these events persisted for more than a day, and it was not necessary to discontinue the intervention in any case.

4. Discussion

We found that a 12-week dual therapy with EMPA and TPM in overweight/obese individuals without diabetes significantly reduced body weight in intervention group (8.9% from baseline) as adjunct to calorie-restricted diet, mean treatment difference between the two groups was 5%. This finding is comparable to the weight loss outcomes achieved with Naltrexone-Bupropion, which is one of the FDA-approved drugs that have been shown to be effective in treating obesity.

Furthermore, a higher proportion of participants in the EMPA-TPM group achieved weight loss of 5% or more compared to the placebo group. It appears that the adaptive increase in energy intake, which may occur as a result of calorie loss through urine, is counteracted by the use of topiramate. In comparison to the placebo group, the intervention group exhibited significant reductions in weight, BMI, and fat mass. However, there was no significant difference observed between the two groups in terms of reductions in WC, fasting lipids and glycemic profiles, blood pressure, or marker of inflammation.

Several studies have reported weight loss as a result of treatment with SGLT2 inhibitors in patients with type 2 diabetes, whether these drugs were administered as monotherapy or in combination with other glucose-lowering medications. Despite causing glycosuria and resulting in energy expenditure, the weight loss induced by SGLT2 inhibitors is typically less than what would be expected. This is due to a compensatory increase in appetite and subsequent caloric intake, which can offset the energy expenditure caused by glycosuria (3). Therefore, in order to achieve substantial weight loss and overcome the counter-regulatory mechanisms that work to maintain body weight, combining SGLT2 inhibitors with medications that utilize different mechanisms of action appears to be the most effective approach (17). In a study (18) among patients with prediabetes, after SGLT2 inhibitor administration (10 mg of oral dapagliflozin, daily, during 12 weeks) there were significant reduces in body weight (80.8 ± 16.3 vs. 77.8 ± 14.9 kg, P = 0.019), BMI (30.3 ± 3.5 vs. 29.2 ± 3.1 kg/m2, P = 0.023), WC (100.6 ± 13.5 vs. 96.2 ± 11.8 cm,

P = 0.003), fasting glucose (5.9 ± 0.4 vs. 5.1 ± 0.3 mmol/L, P < 0.001), with a tendency to increase the insulin sensitivity (1.94 ± 0.72 vs. 2.63 ± 1.04, P = 0.064). Additionally, the researchers did not observe any significant changes in HbA1C or lipid profile. There is a limited amount of research that has investigated the impact of SGLT2 inhibitors on weight loss among obese individuals who do not have diabetes or prediabetes. Bays et al. conducted a study in which canagliflozin 100 mg was administered as a standalone treatment to obese and non-diabetic individuals, resulting in a reduction in body weight of 2.8 kg (19). When SGLT2 inhibitors and GLP1-RA were administered in combination to obese and non-diabetic individuals, body weight decreased by 4.5 kg over a 24-week period. This weight loss was sustained for one year, with a total reduction of 5.7 kg (20, 21). In another study, co-administration of canagliflozin and phentermine, an appetite-suppressing drug with amphetamine-like properties, resulted in significantly greater weight loss than a placebo over 26 weeks (-7.3 kg vs. -0.6 kg) (22). According to our recent meta-analysis (23) SGLT2 inhibitors lowered BMI (WMD = -0.47 [95% CI: -0.63, − .31]; P < .001), and WC (WMD = -3.25 [95% CI: -6.36, -0.14]; P = 0.04), but did not show a significant influence on BP, lipid, and glucose profiles of overweight/obese patients compared to the control groups.

Given that the reduction of lean tissue in obese adults has less favorable effects than the reduction of fat tissue, particularly visceral fat deposits with ectopic effects, it is crucial to consider the type of tissue that is impacted by treatment with SGLT2 inhibitors. According to the findings of a study (24), treatment with dapagliflozin/exenatide led to a notable decrease in subcutaneous and visceral adipose tissue in the abdomen, without any impact on fat-free tissue, as compared to the placebo group. In another study, it was found that daily treatment with dapagliflozin (10 mg) and metformin resulted in weight loss that consisted of two-thirds fat mass and one-third lean mass (25). In our investigation, it was observed that the decrease in fat mass was greater than that of fat-free mass.

SGLT2 inhibitors have been shown to reduce plasma levels of glucose and insulin, while increasing fasting and postprandial glucagon concentrations in patients with type 2 diabetes or obesity without diabetes, due to the glycosuria they induce. A reduction in bloodstream glucose levels, coupled with hormonal changes, can trigger the mobilization of stored fat (26). As a result, there are alterations in the utilization of energy substrates, which can prompt an increase in the use of lipids for energy production (27). The reduction in the insulin-to-glucagon ratio in the portal system can lead to an increase in lipolysis in adipose tissue. Subsequently, non-esterified fatty acids are converted to ketone bodies in the liver via mitochondrial beta-oxidation and ketogenesis, which can result in a metabolic state similar to prolonged starvation (28).

Studies conducted on rodents have shown that SGLT2 inhibitors can reduce inflammation in adipose tissue and increase the amount of brown adipose tissue (29, 30). Given that low-grade chronic inflammation in adipose tissue is a significant contributor to the development of obesity-related complications, such as insulin resistance and type 2 diabetes, reducing inflammation in adipose tissue is of particular importance in the treatment of obesity (31). Although both groups exhibited a significant reduction in CRP levels by the end of the trial, there was no significant difference observed between the

two groups in our study. It is possible that the short duration of the intervention or the relatively small sample size of the study may have contributed to this finding.

Consistent with our findings, Bays et al. (32) reported that canagliflozin did not result in significant alterations in hip circumference, waist circumference, or waist-to-hip ratio compared to a placebo. When compared to a placebo, canagliflozin did not result in clinically significant modifications to glycemic and lipid profiles, nor did it impact blood pressure. The lack of a significant change in the glucose profile observed in our study may be attributed to the fact that reductions in HbA1C levels are typically more pronounced in patients with type 2 diabetes, who exhibit higher baseline levels. Moreover, our study did not reveal any significant changes in lipid profiles. Consequently, the impact of SGLT2 inhibitors on lipid levels is still uncertain.

High blood pressure is a significant comorbidity commonly associated with obesity (3). Weight loss can reverse numerous pathophysiological mechanisms that contribute to hypertension associated with obesity. Thus, a treatment approach that promotes weight loss, reduces hypertension, and has the potential to improve glucose metabolism appears to be a reasonable strategy. In the present study, more reduction in DBP was observed in EMPA/TPM group (8.12 ± 0.21 vs. 8.64 ± 0.57) compared to placebo (8.05 ± 0.13 vs. 8.30 ± 0.45). As expected, individuals who lost more than 5% or 10% of their body weight exhibited a greater reduction in blood pressure. While SGLT2 inhibitors are not currently approved as antihypertensive drugs, multiple clinical trials have demonstrated reductions in systolic and diastolic blood pressure of 3–7 mmHg and 2 mmHg, respectively, following treatment with these medications (26, 33). The precise mechanism by which SGLT2 inhibitors reduce blood pressure is not yet fully understood. However, it is believed that factors such as weight loss, diuretic effects, and a decrease in sympathetic activity may all play a role in this process (3).

On the other hand, in animal models of obesity, TPM has been shown to reduce weight gain in a manner that is dependent on the dosage administered (34, 35). In clinical trials, TPM treatment has been associated with weight loss in patients with epilepsy (36), bipolar disorder (37), and binge eating disorders (38). In a study aimed at investigating the long-term efficacy and safety of TPM in obese subjects (39), weight loss of 5% or more compared to baseline weight was observed in 18% of subjects in the placebo group, compared to 54, 61, 54, and 61 subjects who received doses of 96, 192, and 256 mg per day, respectively; weight loss of 10% or more was reported in 6% of patients in the placebo group compared to 29, 40, and 44 who received the stated doses, respectively ($P < 0.001$). Weight loss was accompanied by significant ameliorations in blood pressure (systolic/diastolic changes of + 0.4/+1.0, -3.1/-1.3, -5.7/-3.4, and − 4.6/-2.4 mmHg were observed for placebo, topiramate 96 mg/day, 192 mg/day, and 256 mg/day, respectively, $P < 0.001$), insulin and glucose. The results of this study demonstrated that the impact of TPM on weight loss was dependent on the dosage administered, and the observed effects were sustained over a period of one year or longer. However, it should be noted that using high doses of TPM for extended periods may result in adverse effects on the central or peripheral nervous system. Therefore, it is not recommended to use high doses of TPM for prolonged periods of time.

The precise mechanism underlying the weight loss induced by topiramate is not yet fully understood. Several animal models (40–42) have demonstrated that administering topiramate can lead to a reduction in appetite and interfere with the efficiency of energy consumption. Topiramate's impact on energy efficiency suggests that it may stimulate the activity of lipoprotein lipase in brown adipose tissue and skeletal muscle (42), which could potentially enhance thermogenesis and substrate oxidation. Furthermore, topiramate has been shown to increase the expression of uncoupling proteins 2 and 3 in adipose tissue and skeletal muscle, leading to a reduction in energy efficiency (41).

As such, the mechanisms of these two drugs may complement each other, and the contribution of each component in the EMPA/TPM combination treatment appears to be additive, and potentially synergistic.

To the best of our knowledge, our study is the first clinical trial to investigate the effects of co-administering EMPA and TPM on anthropometric and metabolic markers in individuals with excess weight but without diabetes. Based on these findings, it may be reasonable to consider the administration of EMPA/TPM in conjunction with a weight loss diet as a potential treatment option for overweight or obese individuals who do not have diabetes. Nevertheless, there are some limitations to our current study. One notable limitation of our study is the absence of an evaluation of hedonic mediators of appetite control, which should be considered in future trials. Since this trial did not include monotherapy comparison groups, it was not feasible to assess the potential additive effects of the treatment. To verify our findings, further long-term studies involving larger sample sizes and lifestyle interventions are necessary.

Conclusion

Administration of EMPA/TPM together with calorie restriction for 12 weeks in overweight patients without diabetes led to a significant reduction in body weight, BMI, and fat mass and was well tolerated by the participants. However, no significant changes were observed in WC, glycemic and lipid profiles, blood pressure, or inflammation between the two groups.

Declarations

Acknowledgments

We acknowledge the contribution of research participants who were involved in this study.

Competing interests

None.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author, MV.

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Author Contributions

B.A. and M.V. designed and wrote the manuscript. A.RA. and F.H. performed interpretation and critical revision of the manuscript. F.H., A.Z. and M.V. critically revised the manuscript. All authors read and approved the final version.

Ethics approval and consent to participate

According to the 2013 Helsinki Declaration guidelines, the protocol of this study was approved by the Medical Ethics Committee of Shahid Beheshti University of Medical Sciences (approval number: IR.SBMU.RETECH.REC.1401.137) and was registered at the Iranian Registry of Clinical Trials (IRCT registration number: IRCT20230114057122N1). All participants signed an informed consent form.

Consent for publication

All authors have given consent for the paper to be published by the corresponding author.

Abbreviations

None.

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Figures

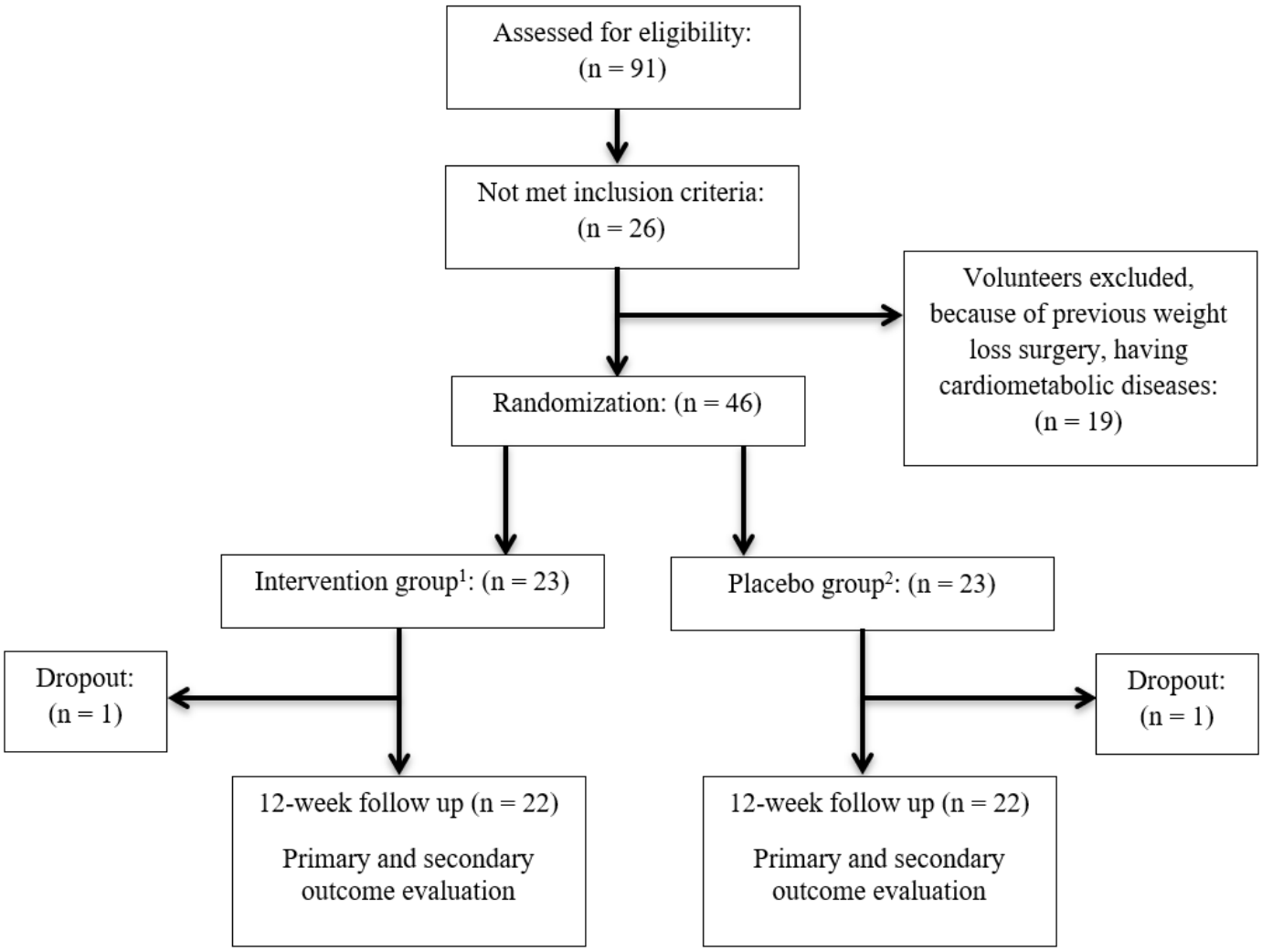
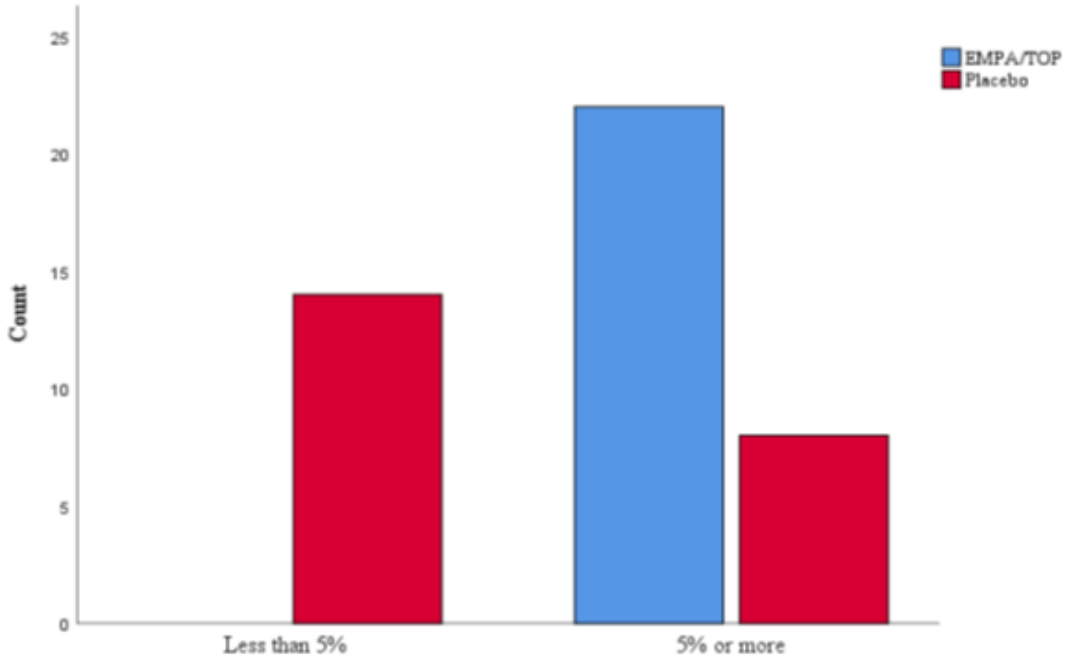


Figure 1

Flow diagram of the study. [1]Participants received a 10 mg Empagliflozin daily plus Topiramate (at the first week 25 mg once a day and from the second week 25 mg twice a day). [2]Participants received an empagliflozin placebo (daily) plus a topiramate placebo (as mentioned for topiramate tablet in group 1).



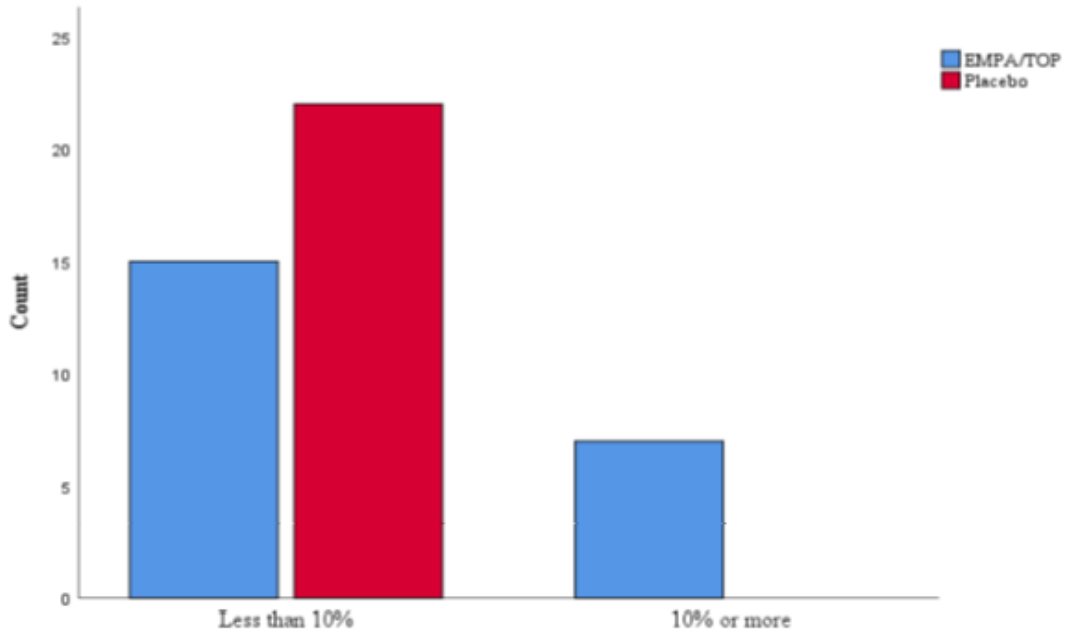


Figure 2

A. The number of subjects with weight loss ≥ 5%.

B. The number of subjects with weight loss ≥ 10%.

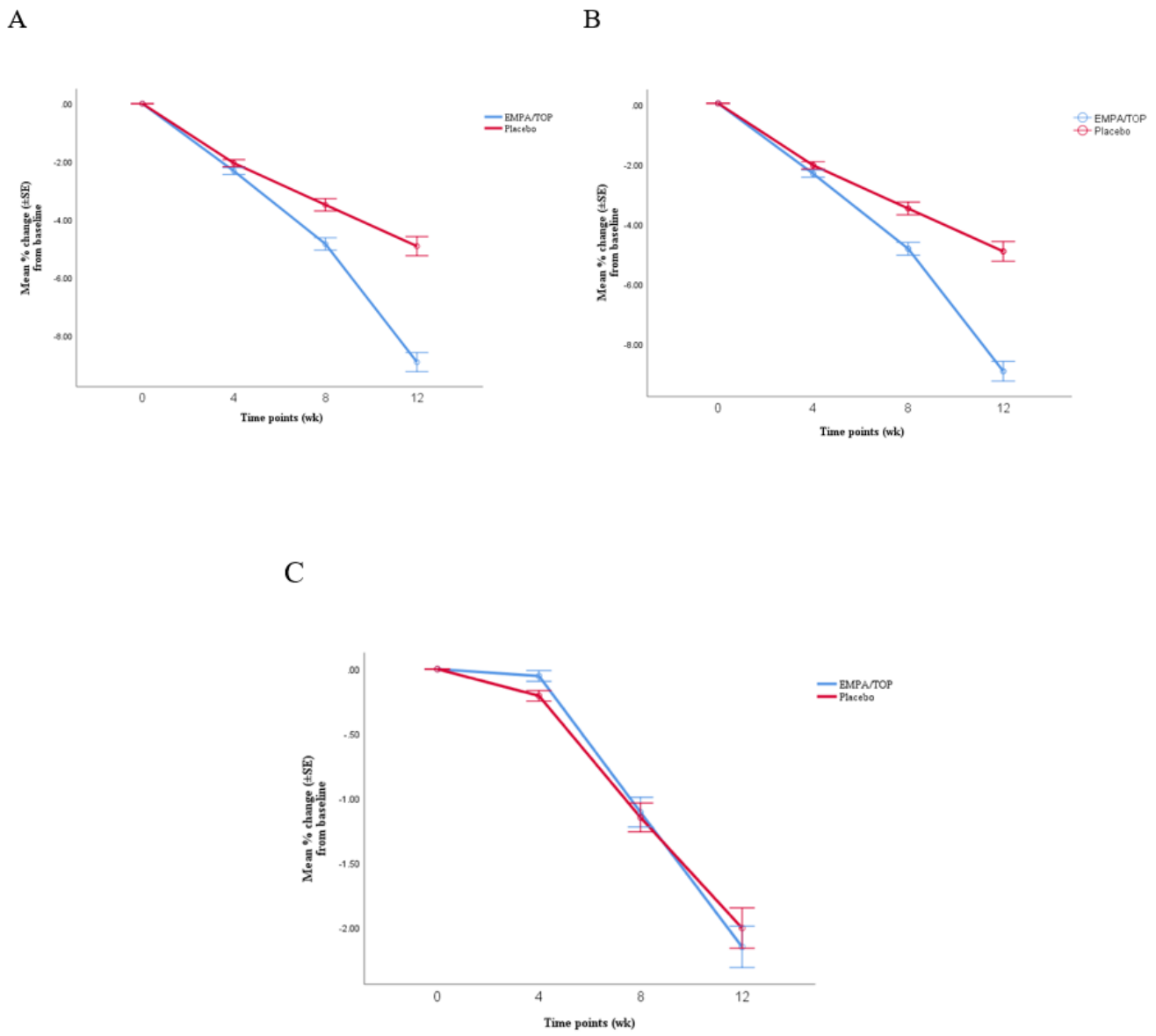


Figure 3

Percent change (± SE) in body weight (A), BMI (B), and waist circumference (C) over time.

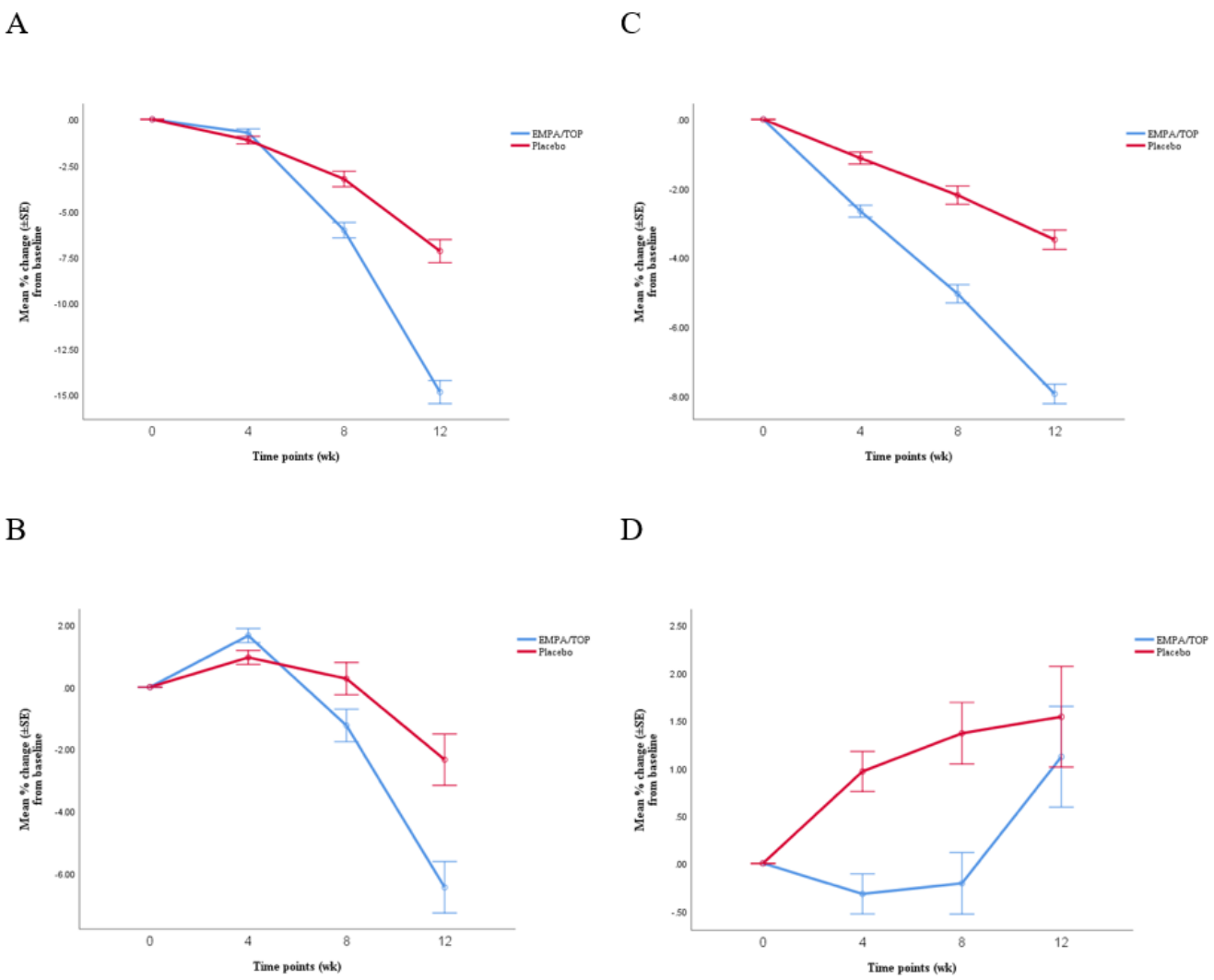


Figure 4

Percent change (± SE) in fat mass (A), body fat percent (B), fat-free mass (C), and body fat-free percent (D) over time.