ETHIOPIAN INTERNATIONAL JOURNAL OF MULTIDISCIPLINARY RESEARCH

eISSN: 2349-5715 pISSN: 2349-5707

Volume: 11, Issue 03, March-2024 SJIF 2019: 4.702 2020: 4.737 2021: 5.071 2022: 4.919 2023: 6.980 2024: 7,662

COMPLEX OF EXERCISE AND GLP-1 RECEPTOR AGONIST TREATMENT REDUCES SEVERITY OF METABOLIC SYNDROME AND INFLAMMATION

Toshmatova G.A.

Andijan State Medical Institute.

Abstract: Identifying and reducing cardiometabolic risks driven by obesity remains a major healthcare challenge [1]. Metabolic syndrome (Metabolic syndrome) is associated with an increased risk of cardiovascular disease, type 2 diabetes, and all-cause mortality [2]. Abdominal obesity is associated with low-grade inflammation and has been proposed as a driver for metabolic syndrome. Body weight loss may improve the factors of Metabolic syndrome [5]; however, weight loss-induced improvements have proven difficult to maintain since substantial weight regain often occurs within the first year [6]. Therefore, investigations of treatment strategies that can maintain, or even reduce, metabolic syndrome, abdominal fat, and low-grade inflammation in currently healthy persons with obesity to prevent future cardiometabolic disease are warranted.

Key words: Metabolic syndrome, risk factors, inflammation,treatment.

Metabolic syndrome denotes a cluster of common risk factors and was intended as an early measure for cardiometabolic disease risk [7]. However, the dichotomous design of Metabolic syndrome has its limitations, and it is debated whether different definitions of Metabolic syndrome add predictive value when adjusted for its individual factors [4]. The newer metabolic syndrome severity z-score (Metabolic syndrome) combines weighted contributions of all Metabolic syndrome factors into a single continuous measure. Studies have shown that individuals within the fourth quartile of Metabolic syndrome scores (> 0.675) had a hazard ratio (HR) of 5.1 for coronary heart disease with more than 11 years of follow-up [8] and 17.4 for future diabetes with a median follow-up of 8 years compared to those from the first quartile of Metabolic syndrome scores. However, Metabolic syndrome has not been investigated in randomized clinical trials comparing treatments during weight loss maintenance in people at risk of future cardiometabolic disease.

High-sensitivity C-reactive protein (hsCRP) is an established biomarker of inflammation [4] and is commonly elevated in persons with obesity [5]. The relationship between hsCRP and the risk of cardiovascular disease is well documented; hsCRP levels of < 1 mg/L, 1–3 mg/L, or > 3 mg/L can be used to classify the risk of cardiovascular risk as low, intermediate, or high (in combination with traditional cardiovascular risk factors) .

Exercise and glucagon-like peptide–1 receptor agonists (GLP-1 RAs) may be different strategies in the primary and secondary prevention of Metabolic syndrome, abdominal fat, and inflammation [7].

A meta-analysis has shown that moderate-to-vigorous aerobic exercise for at least 12 weeks can improve the factors of Metabolic syndrome, and a study of self-reported physical activity has shown that exercise was associated with reduced inflammation markers in 10 years of follow-up [9]. The potential anti-inflammatory effects of exercise might, in part, be due to reduced visceral fat independent of total body weight loss [4]. However, determining the effects of exercise interventions is often complicated by high study heterogeneity and, importantly, varying adherence to intervention protocols [10]. Thus, studies that assess the effects of exercise adherent to intervention protocols are limited.

The GLP-1 RA, liraglutide, approved for obesity therapy, induces weight loss and improves glycemic control and cardiovascular risk factors (e.g., lipid profile and blood pressure) [20, 21]. GLP-1 RAs

eISSN: 2349-5715 pISSN: 2349-5707
Volume: 11, Issue 03, March-2024 SJIF 2019: 4.702 2020: 4.737 2021: 5.071 2022: 4.919 2023: 6.980 2024: 7,662

are also suggested to lower inflammation due to direct anti-inflammatory effects on various tissues and immune cells and partly because of the weight loss seen with GLP-1 RA treatment [11].
We recently showed that a diet-induced 12% weight loss was maintained after one year with either exercise or liraglutide treatment. Combining the two treatments led to additional weight loss, while the placebo group regained body weight [12]. In the present study, we investigated the effects of actually performed moderate-to-vigorous exercise, liraglutide 3.0 mg/day, or the combination of exercise and liraglutide on Metabolic syndrome, abdominal obesity, and the inflammation marker hsCRP in a one-year maintenance period following a diet-induced weight loss. Details on methods and results regarding the primary endpoint (change in body weight) and a secondary endpoint (change in total body fat percentage) have previously been published [24]. This study presents the analysis of the prespecified secondary endpoint Metabolic syndrome, and android fat and hsCRP.
Included participants were asked to complete a low-calorie diet for eight weeks before being randomized to either exercise, pharmacological treatment with liraglutide, the combination of exercise and liraglutide, or placebo for one year. All participants attended 12 individual consultations to support weight loss maintenance after randomization.
Recruited participants were adults living with obesity (18–65 years of age, BMI 32–43 kg/m^2). Major exclusion criteria were any known serious chronic illness, including type 1 or 2 diabetes (see the full list of exclusion criteria in the protocol article of the trial [12]. A total of 215 participants were enrolled in the trial, of which 195 completed the low-calorie diet and were randomized (week 0) in a 1:1:1:1 ratio stratified by sex (male/female) and age ($</\geq 40$ years) to placebo (n = 49); exercise (n = 48); liraglutide (n = 49); liraglutide and exercise (n = 49) for one year [12]. Continuous variables are summarized as means with ± standard deviations (± SD) or medians with interquartile range. Continuous outcomes with repeated measures were analyzed using a mixed linear model in the per-protocol population (i.e., the 130 participants adherent to the prescribed interventions), which might provide a better mechanistic understanding of the interventions, and in the intention-to-treat population (i.e., all 195 participants randomized). Significance testing was performed using $\alpha = 0.05$ on Metabolic syndrome, android fat percentage, and hsCRP outcomes. The following fixed effects were included in the model: time (factorial), group, age group ($</\geq 40$ years), sex, a time-group interaction, and a repeated effect for visit. A supplementary analysis further adjusting for blood pressure or lipid-lowering medication, smoking, and alcohol consumption at inclusion was also performed. All missing data were assumed to be missing at random. The analyses were unadjusted for multiplicity; therefore, definite inferences cannot be made. Results are reported as estimated changes with 95% confidence intervals (95% CI). Statistical sample size power analysis has previously been published and was based on body weight change (a 4 kg difference between the four groups was estimated to require at least 30 participants per group)

Results. A total of 166 participants (85%) completed the study by attending final assessments at week 52. Thus, 15% were lost to follow-up (placebo: 9, exercise: 8, liraglutide: 8,). Overall, there was an even pattern of loss to follow-up, and the most common cause of dropout was personal life conditions (e.g., job-related changes). The per-protocol population included 130 participants (placebo = 39; exercise = 26, liraglutide = 36; combination = 29).
Changes in body weight and total body fat percentage have previously been published [11]. In summary, results from the trial show that after the low-calorie diet, the participants had reduced body weight by 13.1 kg (~ 12%), After one year, the placebo group had increased body weight. The exercise and liraglutide groups maintained body weight while lowering the total fat percentage. The combination group decreased body weight and fat percentage. The median concentration of the

eISSN: 2349-5715 pISSN: 2349-5707
Volume: 11, Issue 03, March-2024 SJIF 2019: 4.702 2020: 4.737 2021: 5.071 2022: 4.919 2023: 6.980 2024: 7,662

inflammation marker hsCRP was 3.8 mg/L before the low-calorie diet and decreased by 32% to 2.4 mg/L after the diet, $P < 0.001$,

After one year, the hsCRP concentrations did not change in the placebo and exercise groups Within the liraglutide group, hsCRP decreased by 36%; however, this decrease was not different from the placebo group. The combination group reduced hsCRP by 43% compared to the placebo group, $P = 0.030$. In the intention-to-treat analysis, hsCRP decreased by 35% within the combination group, but this change was not different from the placebo group

Disscusion. Identifying and managing the risk of cardiometabolic disease associated with obesity remains a major healthcare challenge. Metabolic syndrome, abdominal obesity, and low-grade inflammation constitute risk factors for future cardiometabolic disease. Therefore, we investigated improvements in metabolic syndrome, abdominal obesity, and low-grade inflammation during exercise, a glucagon-like peptide 1 receptor agonist, or the combination of the two following an eight-week low-calorie diet.

The diet-induced weight loss reduced Metabolic syndrome, abdominal obesity, and inflammation marker hsCRP. After one year, the combination of exercise and liraglutide treatment reduced Metabolic syndrome, android fat percentage, and hsCRP compared to placebo. Exercise treatment maintained Metabolic syndrome and hsCRP and reduced android fat percentage compared to placebo. Liraglutide treatment reduced Metabolic syndrome and android fat percentage while maintaining hsCRP compared to placebo. Placebo treatment was associated with maintenance of the diet-induced reductions in Metabolic syndrome, hsCRP, and android fat percentage, even though 50% of the weight lost during the low-calorie diet was regained in the placebo group, while Metabolic syndrome prevalence and fat masses increased again. In addition, we have previously reported that the placebo group became sedentary one year after the initial weight loss

Conclusion. In people with obesity at risk of developing cardiometabolic disease, the low-calorie diet improved Metabolic syndrome, abdominal obesity, and inflammation marker hsCRP. After one year, intervention with exercise further reduced abdominal obesity, liraglutide treatment further reduced Metabolic syndrome and abdominal obesity, and liraglutide combined with adherent exercise further reduced Metabolic syndrome.

References:

1. Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association task force on practice guidelines and the obesity society. J Am Coll Cardiol. 2014;63(25):2985–3023.
2. Wilson PW, D'Agostino RB, Parise H, Sullivan L, Meigs JB. Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. Circulation. 2005;112(20):3066–72.
3. Mottillo S, Filion KB, Genest J, Joseph L, Pilote L, Poirier P, et al. The metabolic syndrome and cardiovascular risk a systematic review and meta-analysis. J Am Coll Cardiol. 2010;56(14):1113–32.
4. Neeland IJ, Ross R, Després J-P, Matsuzawa Y, Yamashita S, Shai I, et al. Visceral and ectopic fat, atherosclerosis, and cardiometabolic disease: a position statement. Lancet Diabetes Endocrinol. 2019;7(9):715–25.
5. Case CC, Jones PH, Nelson K, O'Brian Smith E, Ballantyne CM. Impact of weight loss on the metabolic syndrome. Diabetes Obes Metab. 2002;4(6):407–14.

eISSN: 2349-5715 pISSN: 2349-5707
Volume: 11, Issue 03, March-2024 SJIF 2019: 4.702 2020: 4.737 2021: 5.071 2022: 4.919 2023: 6.980 2024: 7,662

6. Nordmo M, Danielsen YS, Nordmo M. The challenge of keeping it off, a descriptive systematic review of high-quality, follow-up studies of obesity treatments. Obes Rev. 2020;21(1): e12949.
7. Mongraw-Chaffin M, Foster MC, Anderson CAM, Burke GL, Haq N, Kalyani RR, et al. Metabolically healthy obesity, transition to metabolic syndrome, and cardiovascular risk. J Am Coll Cardiol. 2018;71(17):1857–65.
8. Alberti KGMM, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome. Circulation. 2009;120(16):1640–5.
9. Drucker DJ. Mechanisms of action and therapeutic application of glucagon-like peptide-1. Cell Metab. 2018;27(4):740–56.
10. Akawi N, Checa A, Antonopoulos AS, Akoumianakis I, Daskalaki E, Kotanidis CP, et al. Fat-secreted ceramides regulate vascular redox state and influence outcomes in patients with cardiovascular disease. J Am Coll Cardiol. 2021;77(20):2494–513.
11. Lundgren JR, Janus C, Jensen SBK, Juhl CR, Olsen LM, Christensen RM, et al. Healthy weight loss maintenance with exercise, liraglutide, or both combined. N Engl J Med. 2021;384(18):1719–30.
12. Jensen SBK, Lundgren JR, Janus C, Juhl CR, Olsen LM, Rosenkilde M, et al. Protocol for a randomised controlled trial of the combined effects of the GLP-1 receptor agonist liraglutide and exercise on maintenance of weight loss and health after a very low-calorie diet. BMJ Open. 2019;9(11): e031431.