Effects of orlistat/phentermine versus phentermine on vascular endothelial cell function in obese and overweight adults: A randomized, double-blind, placebo-controlled trial

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Directed by Professor Lee Ji Won

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This manuscript is dedicated to my dear husband and my beautiful daughter, Sohee, who always support me.

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ABSTRACT

Effects of orlistat/phentermine versus phentermine on vascular endothelial cell function in obese and overweight adults: A randomized, double-blind, placebo-controlled trial

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Background: Obesity is a significant risk factor for increased morbidity and mortality associated with cardiovascular disease (CVD) and other chronic diseases. The endothelium controls micro and macrovascular circulation. Obesity leads to endothelial cell dysfunction which often precedes irreversible atherosclerotic CVD. Although weight reduction decreases cardiovascular risk, several anti-obesity drugs pose concerns for cardiovascular safety. Orlistat, a strong lipase inhibitor, is effective in reducing CVD risk factors such as blood glucose and cholesterol in obese adults. This study aimed to compare the efficacy and effectiveness of concomitant administration of orlistat and phentermine versus phentermine alone on endothelial cell function in overweight and obese adults with back pain.

Methods: We conducted a 12-week, double blinded, placebo-controlled clinical trial involving 114 patients with a body mass index (BMI) of at least 30 or over or a BMI of at least 27 or over with weight-related comorbidities. We randomly assigned patients

in a 1:1 ratio to receive orlistat (120 mg) three times daily and phentermine (37.5 mg) once daily, or a placebo three times daily and phentermine (37.5 mg) once daily. Both groups were instructed to intake a calorie reduced diet and undertake light to moderate exercise. Primary endpoint was changes in endothelium dependent vasodilatation measured by ultrasound assessment of flow mediated dilatation (FMD). Differences within groups after intervention were compared using the paired t-test or Wilcoxon signed rank test. Differences of changes between groups were calculated using an analysis of covariance after adjusting for each baseline value.

Results: Mean weight loss during the 12-week study period was 6.1 kg in the orlistat/phentermine group and 6.0 kg in the placebo/phentermine group. Adjusted mean changes in total cholesterol (TC) and non-high density cholesterol (HDL-C) were significantly greater in the orlistat/phentermine group than the placebo/phentermine group (difference of TC: -0.62±0.07 mmol/l vs. -0.32±0.07 mmol/l, respectively, p=0.005; difference of non-HDL-C: -0.53±0.07 mmol/l vs. -0.30±0.07 mmol/l, respectively, p=0.016). Adjusted mean changes in endothelium dependent FMD were significantly greater in the orlistat/phentermine group than the placebo/phentermine group (4.97±0.98% vs. 2.05±0.99%, respectively; p=0.038). Changes in endothelium-independent NMD were not significantly different between groups.

Conclusion: Orlistat/phentermine significantly improved vascular endothelial cell function compared to phentermine alone. Orlistat taken concomitantly with phentermine may decrease the risk of cardiovascular disease, especially in overweight and obese patients with comorbidities.

Key words: orlistat; phentermine; obesity; back pain; cholesterol; endothelial cell function

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I. INTRODUCTION

The prevalence of obesity is gradually increasing globally.[1] In Korean, the prevalence of obesity increased from 29.7% in 2009 to 32.4% in 2015.[2] Obesity is defined as abnormal and excessive fat accumulation that may worsen health.[3] Obesity is closely link to insulin resistance, inflammation, activated sympathetic nerve system, dyslipidemia, and cardiac complications.[1,4,5] The endothelium, which is comprised of a monolayer of endothelial cells, maintains vascular homeostasis by producing and releasing vasoactive molecules.[6] When the vessel is under shear stress, a calcium-activated potassium channel in the endothelium is opened which activates endothelial

nitric oxide synthase (eNOS) and leads to an increase of NO.[7] Phosphorylation of eNOS by Akt is also involved in the Ca2+-independent regulatory mechanism and the activation of eNOS.[8] In a prolonged state of shear stress, eNOS gene transcription alters to regulate output of NO.[7] Endothelial cell dysfunction is a pathological status which covers all maladaptive changes, including the down-regulation of the bioavailability of nitric oxide, and increased proinflammatory cytokines and adhesion molecules.[9,10] Because the endothelium regulates the micro and macro circulation of blood flow, endothelial dysfunction is considered to be an early indicator of cardiovascular diseases (CVD).[9,10] Obesity and its related comorbidities, such as hypertension and hypercholesterolemia, are risk factors of endothelial cell dysfunction.[11] Weight loss, or metabolic parameter improvement regardless of weight loss, ameliorate endothelial cell function.[12-14] Lifestyle modifications, consisting of reduced calorie intake, physical activity, and behavior interventions, should be the first approach to treating obesity.[15,16]

Recently, obesity or overweight has been reported to be closely associated with lower back pain.[17] Obese people with lower back pain face physical limitations.[18] Physical inactivity over the long time further physical function decline and obesity.[18] Therefore, concurrent initiation of pharmacotherapy could be recommended in overweight or obese patients with weight-related complications that may be improved by weight loss.[16,19,20]

Anti-obesity drugs can be divided into two mechanisms: central acting mechanism (appetite suppressants) and peripheral acting mechanism (acting on the gastrointestinal tract).[21,22] Despite being effective for weight loss, several appetite suppressants (i.e.

fenfluramine, dexfenfluramine, and sibutramine) were withdrawn from market due to associated cardiovascular risks.[21,23]

As a result, the US Food and Drug Administration (FDA) now require newly developed anti-obesity drugs to demonstrate efficacy and safety, including an acceptable cardiovascular safety profile.[23] Combination anti-obesity drugs which have different mechanisms (i.e.. phentermine plus topiramate and naltrexone plus bupropion) have attracted a great interest because of their improved efficacy and safety.[23-25]

Phentermine hydrochloride (HCl), a sympathomimetic amine, was approved for short-term use (up to 12 weeks) of obesity treatment.[21] Phentermine is the most commonly prescribed anti-obesity drug in the United State, and other countries.[26,27] Phentermine's efficacy has been demonstrated in terms of weight loss and improved metabolic parameters without clinically severe adverse events.[28,29] However, concerns still remain about the associated stimulant-like side effects resulting from its sympathomimetic pharmacology, including increased heart rate (HR) and blood pressure (BP).[22]

Orlistat, a gastrointestinal (GI) lipase inhibitor, is a long-term approved anti-obesity medication which acts on the GI tract; not the central nervous system.[30,31] Treatment of obesity with orlistat combined with lifestyle modification has demonstrated metabolic benefits such as lowering blood sugar levels and BP, as well as improving the lipid profile by inhibiting fat absorption.[31-33] In addition, several studies have noted the antioxidant and anti-tumor effects of orlistat.[34,35] We expect these metabolic benefits to reduce the cardiovascular side effects of previous obesity drugs.

Owing to their differing pharmacology, concomitant treatment of orlistat with

phentermine is commonly used off-label in clinical practice.[36] However, there have been no clinical trials to assess whether the concomitant administration of these two drugs improves metabolic parameters in addition to weight loss. We hypothesized that adding orlistat to phentermine improves endothelial cell function compared to phentermine alone in obese and overweight adults with weight-related comorbidities and lower back pain.

II. METHOD

1. Study design and patients

This study was a randomized, double-blind, placebo-controlled 12-week clinical trial. The protocol was approved by the institutional review boards of Yongin Severance Hospital (IRB No. 9-2018-0004) and registered with ClinicalTrails.gov (number: NCT03675191). This study was performed in compliance with the Declaration of Helsinki.

Patients were recruited from October 2018 to May 2019 at Yongin Severance Hospital (Yongin, South Korea). Eligible patients, aged 20-70 years, were obese (body mass index [BMI]≥30 kg/m^2) or overweight (BMI≥27 kg/m^2) with at least one weight-related complication (e.g. diabetes, prediabetes, hypertension, dyslipidemia, or metabolic syndrome).[16] Patients had lower back pain that limited the implementation and effectiveness of exercise, with visual analog scale (VAS) score more than 3. Exclusion criteria included the following contraindications for use of phentermine or orlistat: progressive atherosclerosis, symptomatic CVD, pulmonary hypertension, valvular

heart diseases, blood pressure (BP) greater than 180/120 mmHg, hyperthyroidism, glaucoma, fasting glucose 11.1 mmol/L, hepatic disease, renal diseases; as well as history of psychiatric illness, taking medications such as monoamine oxidase inhibitors within 14 days of screening, pregnancy, breast feeding, loss of more than 5 kg within three months, and treatment with other anti-obesity medication within one year. Written consent from was obtained from all patients prior to participation.

2. Randomization and masking

Participants were randomly assigned in a 1:1 ratio to receive a placebo three times a day plus phentermine hydrochloride (37.5 mg) once daily or orlistat (120 mg) three times a day plus phentermine hydrochloride (37.5 mg) once daily. Subjects were instructed that if they a skipped meal, they should also skip the corresponding orlistat dose. Randomization was performed using a centralized computer-generated system. Investigators and patients were masked to treatment assignment throughout the study. Active drug and placebo capsules were identical in appearance and produced by the study sponsor (Hanmi Pharmaceutical Co. Ltd). Of the initial 114 participants assessed for eligibility, one patient was excluded at screening due to an incidental diagnosis of atrial septal defect. A total of 113 participants were enrolled in this study. After undergoing 1:1 ratio randomization, 56 subjects were assigned to receive placebo plus phentermine (placebo/phentermine group) and 57 subjects were assigned to receive orlistat plus phentermine (orlistat/phentermine group). One participant assigned to the placebo/phentermine group withdrew consent before allocating receiving intervention

(Figure 1). Five participants in placebo/phentermine group and three participants in orlistat/phentermine group did not reach contact after first or second visit. Each four participants withdrew consent during clinical trials due to adverse event. This study was completed by 46 participants in the placebo/phentermine group and 50 participants in the orlistat/phentermine group.

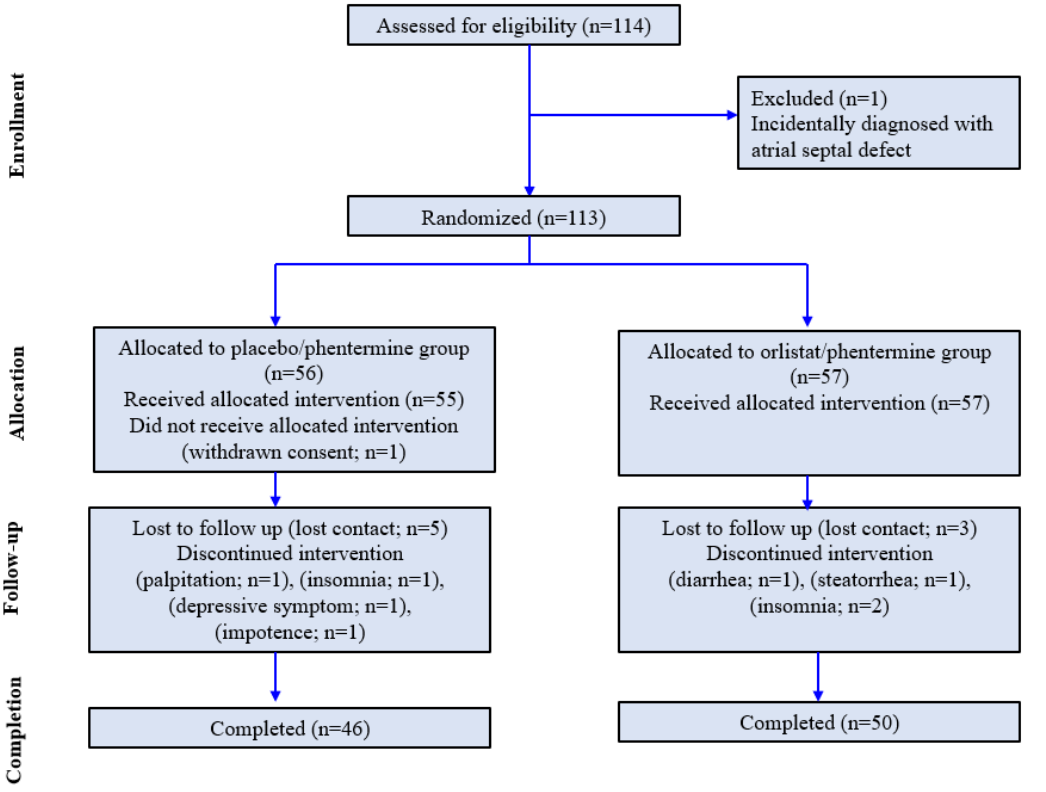


Figure 1. Flow chart of study cohort enrollment, allocation, follow-up and completion

3. Procedures and endpoints

Study visits were scheduled at screening, baseline, and at 4, 8, and 12 weeks. Body weight, waist circumference (WC), systolic blood pressure (SBP), and diastolic blood pressure (DBP) were measured at each visit. Laboratory tests, heart rate variability (HRV), body composition measurement, and FMD were measured at baseline and 12 weeks. Health-related (physical activity, smoking, alcohol consumption) and food intake (using a 24-hour recall method) questionnaires were administered at baseline and 12 weeks. Participants were categorized into never smoker, ex-smoker, and current smoker groups. An alcohol drinker was defined as a person who drinks alcohol more than once a month. Physical activity was defined as undertaking light to moderate exercise (e.g. brisk walking, gardening, hiking, bicycling 5-9 mph, aqua aerobic) more than two times per week. We used a binary variable with the presence or absence of history of hypertension, dyslipidemia, or diabetes, according to a self-reported questionnaire.

We assessed VAS score and Oswestry Disability Index (ODI) at screening and 12 weeks. The VAS score is a validated pain rating scale by recording with a handwritten mark on a 10cm line that represents a continuum between no pain (0cm) and worst pain (10cm).[37] The ODI is a self-administered questionnaire to quantify disability related to lower back pain.[38] It comprises of ten questions related to pain, lifting, ability to care for oneself, ability to walk, ability to sit, sexual function, ability to stand, social life, sleep quality, and ability to travel. Each question is scored from 0 to 5 and the total score is multiplied by 2.

Body composition (weight, skeletal muscle mass, fat mass, body fat percentage, and

waist to hip ratio [WHR]) was assessed via bioelectrical impedance analysis using the Inbody720 body composition analyzer (Biospace, Seoul, South Korea). Waist circumference was measured using a measuring tape on the horizontal plane midway between the lowest rib and the iliac crest.

Blood samples were obtained after more than eight hours fasting. White blood cell (WBC) counts were quantified by flow cytometry using a XN2000 (Sysmex, Kobe, Japan). Insulin levels were analyzed by chemiluminescent microparticle immunoassay using an Architect i2000SR (Abbott, Abbott park, IL, USA). Lipids (total cholesterol [TC], low-density lipoprotein cholesterol [LDL-C], non-high-density lipoprotein cholesterol [non-HDL-C], triglyceride [TG], HDL-C) were analyzed enzymatic color test. C-reactive protein (CRP) was analyzed using an Immuno-turbidimetric method. The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using the following equation: fasting glucose (mmol/L)× fasting insulin (uU/mL)/22.5. At every visit, all participants were consulted about diet and exercise by a doctor and advised to follow a hypocaloric diet (consuming 500 kcal below individual estimated energy requirements per day) and light (~3 MET) to moderate intensity exercise more (3~6 MET) than three time per week.

The primary efficacy endpoint was change of flow mediated dilation (FMD) based on ultrasound assessment. Secondary endpoints were change in weight, WC, BMI, fat mass, fat, percentage, lipids (TC, non-HDL-C, LDL-C, TG), CRP, glycemic variables (fasting glucose, fasting insulin, HOMA-IR), and VAS and ODI of lower back pain.

4. Safety and compliance

Safety assessment consisted of assessment of adverse events and use of concomitant medications, measurement of vital signs (SBP and DBP, HR), laboratory tests (AST, ALT, Cr), and echocardiography. Adverse event and use of concomitant medications were checked at every visit and vital signs were measured at every visit. Mean HR was recorded at baseline and 12 weeks using a heart rate variability analyzer with a 3-lead ECG (MEDICORE, Gyeonggi, Korea) for five minutes, in the supine position, in a quiet room.

A trained and certified sonographer conducted all echocardiography using the SSH-880CV ultrasound system (Artida, Tokyo, Japan) at screening and 12 weeks. A cardiologist supervised and interpreted the results. Two-dimensional and M-mode echocardiography, and conventional doppler echocardiography data were obtained. The echocardiography checklist included chamber size, hypertrophy, right ventricular function, left ventricular systolic function, left ventricular diastolic function, valves, atrial or ventricular septal defects, thrombus, mass, and other incidental findings.

Drug compliance was measured by counting the remaining pills at every visit. Compliance rate was set at more than 70%. For orlistat, the compliance rate was determined after taking the number of meals skipped into consideration.

5. Assessment of vascular endothelial cell function

Endothelium-dependent FMD was assessed according to the guidelines for ultrasound assessment of endothelial-dependent flow mediated vasodilatation of the brachial artery

introduced by the International Brachial Artery Reactivity Task Force.[7] A B-mode ultrasound with a 7.5 MHz linear array transducer (Acuson, SIEMENS sequoia C 512; Mountain View, CA, USA) was used to assess brachial artery diameter. Flow mediated dilatation was conducted after 8 hr to 12 hr fasting in a quiet, temperature-controlled room. Patients were not permitted to take antihypertensive medication (calcium channel blocker, nitrate, beta-blocker, angiotensin-converting-enzyme inhibitor, angiotensin II receptor blockers) within 48 hr before the FMD. Patients were not permitted caffeine or smoking within 8 hours. A sphygmomanometer cuff was placed above the antecubital fossa on the forearm and inflated to at least 50 mmHg above patients' SBP. Images of the brachial artery were recorded before inflation and 30 second (s), 45 s, 60 s, 75 s, and 90 s after deflation of the cuff. After 10 minutes rest, 0.6 mg sublingual nitroglycerin was administered and endothelium independent dilatation was assessed. Images were obtained before nitroglycerin administration and at 3 and 4minutes post nitroglycerin administration. Vessel diameter was measured at the end diastole incident (at the R-wave) on electrocardiogram (ECG). Endothelium dependent (FMD) and independent vasodilatation (NMD) were calculated as follows: FMD (%) or NMD (%) = ([maximal diameter-baseline diameter]/baseline diameter)×100. The same blinded investigator performed all FMD assessments. The intraclass correlation coefficient was 0.979 (0.970-0.985).

6. Statistical analysis

We conducted the Kolmogorov-Smirnov test of normality to test the normal

distribution of values before analysis. Data are presented as mean± standard deviations (SDs) or median (interquartile ranges [IQR]). For efficacy analyses we used data from the full analysis set, which included all patients who underwent randomization and had at least one assessment. Missing values were imputed using the last-observation-carried-forward method.

Differences in baseline characteristics between placebo/phentermine and orlistat/phentermine were compared using the independent t-test or Mann Whitney U test. Differences after intervention within groups were compared using the paired t-test or Wilcoxon signed rank test. Differences in changes between groups were calculated using an analysis of covariance after adjusting for each baseline value. Significance tests were two-sided, with an alpha value of 0.05. All statistical analyses were performed using SPSS software version 25.0 (IBM Corp., Armonk, NY, USA).

For calculation of sample size, there was no RCT to investigate the effect of orlistat on endothelial cell function using the FMD. Because LDL-C was significantly correlated with FMD in previous studies,[39,40] we calculated the effect size based on absolute LDL-C changes between the orlistat group (-0.53±0.65) and the placebo/phentermine group (-0.09±0.8; effect size=0.6).[41] We assumed that the effect size would be similar to the effect size of FMD. Cohen's effect size 0.6 indicates a medium to large effect size. Sample size was calculated using an independent two sample t-test with 80% power, a two-sided significance level of 5%, and a dropout rate of 20%.

III. RESULTS

Of the 113 patients who participated in this study, 77.9% were female. Rates of study drop-out were similar between groups. Baseline characteristics were similar between the orlistat/phentermine group (n=57) and the placebo/phentermine group (n=55) in terms of age (45.5±12.5 years vs. 46.0±11.3 years, respectively; p =0.839), gender (44 female vs. 44 female; p=0.860), and BMI (30.8 (28.1, 33.5) vs. 29.8 (27.6, 33.6); p=0.416) (Table 1).

Table 1. Baseline characteristics of study participants

	Placebo/phentermine	**Orlistat/phentermine**	**P-value**
N (%)	55 (49.6)	57 (50.4)	
Sex (female)	43 (78.6)	44 (77.2)	0.860
Age, years	46.0 ± 11.3	45.5 ± 12.5	0.839
Physical measurement			
Height, cm	163.0 ± 9.0	164.0 ± 9.6	0.561
Weight†, kg	78.3 (72.2, 90.5)	80.3 (72.6, 96.3)	0.562
Body mass index, kg/m^2†	29.8 (27.6, 33.6)	30.8 (28.1, 33.5)	0.416
Waist circumference, cm	102.8 ± 9.5	104.1 ± 9.5	0.473
Skeletal muscle mass, kg†	26.0 (23.4, 30.0)	26.4 (22.9, 33.0)	0.688
Fat mass, kg†	30.5 (28.5, 37.1)	32.4 (28.0, 39.5)	0.522
Fat percentage, %	39.9 ± 5.7	40.0 ± 6.9	0.985
WHR†	0.95 (0.93, 0.97)	0.95 (0.93, 0.98)	0.733
SBP (mmHg)	128.6 ± 14.2	127.8 ± 15.5	0.785
DBP (mmHg)	86.3 ± 12.5	85.6 ± 11.7	0.781
Mean heart rate (bpm)	72.8 ± 8.8	71.8 ± 9.5	0.545

Comorbid condition, n (%)			
HTN	33 (58.9)	30 (52.6)	0.500
Diabetes	6 (10.7)	12 (21.1)	0.133
Hypercholesterolemia	22 (39.3)	16 (28.1)	0.207
Drug history			
HTN medication	13 (23.2)	11 (19.3)	0.611
Diabetes medication	4 (7.1)	6 (10.5)	0.527
Dyslipidemia medication	13 (23.2)	9 (15.8)	0.319
Health related behavior			
Physical activity, n (%)	11 (19.6)	10 (17.5)	0.482
Smoking, n (%)			0.719
Non-smoker	30 (66.7)	35 (70.0)	
Ex-smoker	8 (17.8)	6 (12.0)	
Current smoker	7 (15.6)	9 (18.0)	
Alcohol consumption, n (%)	21 (47.7)	26 (54.2)	0.537
Back pain, VAS score†	4.0 (3.0, 5.0)	4.0 (3.0, 5.0)	0.203
Total calorie intake (kcal)	1522.7 (1160.2, 1739.2)	1458.7 (1238.8, 1294.6)	0.692

Data are presented as mean±standard deviations, median (interquartile ranges), or number (percentage).

P-values calculated using independent two sample t-test or Mann Whitney U test.

† Continuous values calculated using Mann Whitney U test and categorical values calculated using chi-square test.

The metabolic parameters and values of FMD were well balanced between groups (Table 2).

Table 2. Metabolic parameters of placebo/phentermine and orlistat/phentermine

groups at baseline

	Placebo/phentermine	Orlistat/phentermine	P-value
Laboratory test			
WBC	6662 ± 173	6577 ± 173	0.794
CRP	1.25 (0.73, 2.08)	1.50 (0.60, 2.70)	0.922
AST	24.0 (19.3, 30.8)	25.0 (19.0, 33.5)	0.573
ALT	25.0 (17.3, 31.8)	25.0 (15.5, 44.0)	0.473
Cr	0.75 (0.68, 0.86)	0.73 (0.68, 0.87)	0.719
Glucose (mmol/l)	5.61 (5.38, 6.11)	5.72 (5.33, 6.43)	0.269
Insulin	8.65 (6.88, 12.98)	8.20 (5.60, 12.85)	0.399
HOMA-IR	2.27 (1.77, 3.49)	2.05 (1.39, 3.66)	0.713
Triglyceride (mmol/l)	1.47 (1.04, 1.78)	1.36 (0.98, 1.68)	0.617
Total cholesterol (mmol/l)	5.33 ± 1.04	5.02 ± 0.92	0.101
LDL cholesterol (mmol/l)	3.40 ± 0.80	3.10 ± 0.62	0.024
Non-HDL cholesterol (mmol/l)	4.00 ± 1.03	3.66 ± 0.88	0.072
HDL cholesterol (mmol/l)	1.34 ± 0.23	1.36 ± 0.33	0.076
Flow mediated dilatation			
FMD (%)	11.2 ± 5.4	10.6 ± 6.1	0.557
NMD (%)	10.4 ± 7.3	9.6 ± 6.2	0.621

P-values calculated using independent two sample t-test or Mann Whitney U test.

The baseline values of TTE are described in Table 3.

Table 3. Characteristics of transthoracic echocardiography of placebo/phentermine and orlistat/phentermine groups at baseline

	Placebo/phentermine	Orlistat/phentermine	P-value
LVEF, %	62.2 ± 4.7	62.6 ± 4.6	0.632
E wave velocity, cm/s	0.52 ± 0.13	0.52 ± 0.14	0.975
A wave velocity, cm/s	0.57 ± 0.11	0.56 ± 0.12	0.474
E/A	0.86 (0.72, 1.14)	0.89 (0.73, 1.17)	0.756
E wave Decel time, ms	150 (150, 180)	150 (150, 170)	0.960
E’	0.06 (0.05, 0.08)	0.06 (0.05, 0.07)	0.936
E/E’	8.3 ± 1.7	8.2 ± 1.8	0.765
LAVI	16.7 ±4.2	18.2 ±4.9	0.081
LVEDD, mm	45.7 ± 3.7	45.8 ± 3.9	0.910
LVESD, mm	31.5 ± 2.9	31.4 ± 3.1	0.902
RVSP	26.2 ± 4.3	26.2 ± 3.1	0.988

P-values calculated using a Mann Whitney U test.

Table 4 shows the characteristics of the two groups before and after intervention. There was significant weight loss in both groups after 12 weeks (-6.1 in orlistat/phentermine vs -6.0kg in placebo/phentermine). All other values regarding body composition such as BMI, WC, fat mass, fat percentage, and WHR were significantly decreased in both groups (all $p<0.001$). Skeletal muscle mass was also significantly decreased in both groups ($p<0.001$). Blood pressure (SBP and DBP) was significantly decreased, and mean heart rate was increased without significance in both groups. Fasting insulin levels and HOMA-IR were significantly decreased in both groups. However, fasting glucose levels were not changed in either groups. Inflammatory marker CRP and TG, TC, LDL-C, and non-HDL-C levels were

significantly decreased in both groups. Whereas, HDL-C levels were significantly decreased in the orlistat/phentermine group only.

Endothelium-dependent FMD was significantly improved in the orlistat/phentermine group only (p<0.001; orlistat/phentermine vs. p=0.098; placebo/phentermine). However, endothelium-independent NMD changes were not improved in either group.

Table 4. Characteristics of placebo/phentermine and orlistat/phentermine groups at baseline and 12 weeks

	Placebo /phentermine		**Orlistat /phentermine**	
	Baseline	**12 weeks**	**Baseline**	**12 weeks**
Physical measurement				
Weight	82.6 ± 16.0	76.5 ±16.4*	84.9 ±16.0	78.8 ±15.3*
Body mass index	31.0 ± 4.2	28.9 ± 4.3*	31.4 ±3.9	29.1 ±3.7*
Waist circumference	102.8 ± 9.5	94.6 ±10.0	104.1 ±9.5	95.0 ±10.3*
Skeletal muscle mass	26.0 (23.4, 30.0)	24.5 (22.9, 28.7)*	26.4 (22.9, 33.0)	25.0 (22.1, 31.2)*
Fat mass	30.5 (28.5, 37.1)	27.6 (23.4, 32.5)*	32.4 (28.0, 39.5)	28.1(24.0, 33.6)*
Fat percentage	39.6(36.2,44.0)*	38.0(32.7,42.6)*	40.1(36.2, 45.3)	37.7 (33.4, 42.4)*
WHR	0.95 90.93, 0.97)	0.93 (0.91, 0.97)*	0.98 (0.93,0.98)	0.94 (0.91, 0.96)*
SBP	128.6 ±14.2	119.5 ±13.1*	127.8 ±15.5	118.9 ±12.8*
DBP	86.3 ±12.5	77.8 ±9.9*	85.6 ±11.7	77.4 ±11.4*
Mean heart rate	72.8 ±8.8	73.2 ± 10.3	71.8 ±9.5	74.1 ±9.9
WBC	6660 ±173	6453 ±1.66	6577 ±173	6639 ±169
CRP	1.2 (0.7,2.1)	1.2 (0.5, 1.5)*	1.5 (0.6, 2.7)	1.0(0.4, 1.75)*
Glucose (mmol/l)	5.6 (5.4, 6.1)	5.6 (5.2, 6.0)	5.7 (5.3, 6.4)	5.7 (5.4, 3.6)
Insulin	9.8 ±4.4	7.8 ±4.2*	9.6 ±5.6	7.8 ±4.4*
HOMA-IR	2.27 (1.77, 3.49)	1.89 (1.13, 2.33)*	2.05(1.39, 3.66)	1.71(1.07,3.11)*
Lipid profiles				
Triglyceride	1.47(1.04,1.78)*	1.13(0.93, 1.47)*	1.36(0.98,1.68)	1.18(0.82, 1.59)*

Total cholesterol	5.33 ±1.04	4.96 ±1.00*	5.02 ±0.92	4.45 ±0.75*
LDL cholesterol	3.40 ±0.80	3.15 ±0.76*	3.10 ±0.62	2.78 ±0.55*
Non-HDL cholesterol	3.99 ±1.04	3.64 ±0.96*	3.66 ±0.88	3.18 ±0.69*
HDL cholesterol	1.33 ± 0.24	1.32 ± 0.23	1.36 ±0.33	1.27 ±0.26*
FMD (%)	11.2±.5.4	13.0±6.6	10.6±6.1	15.8±8.2*
NMD (%)	12.7±6.3	14.3±6.0	11.0±5.5	13.0±6.3
Back pain, VAS score	4.0 (3.0, 5.0)	3.0 (2.0, 5.0)*	4.0 (3.0, 5.0)	3.0 (2.0, 4.5)*
Total calorie intake	1547.2 ± 567.6	1093.2 ± 473.4*	1661.3 ± 664.1	1249.7 ± 448.9*

Adjusted mean changes in anthropometric measurements (weight, BMI, WC, fat mass, fat percentage), BP, CRP, insulin, and HOMA-IR were not different between groups (Table 5).

Table 5. Changes of mean ± standard error of metabolic parameters in placebo/phentermine and orlistat/phentermine groups from baseline to 12 weeks

	Placebo/phentermine	**Orlistat/phentermine**	**p-value**
Physical measurement			
Weight	-6.2±0.6	-6.0±0.6	0.941
Body mass index†	-2.1±0.2	-2.3±0.2	0.510
Waist circumference†	-8.6±0.8	-9.0±0.8	0.751
Skeletal muscle mass	-1.08±0.18	-1.04±0.18	0.889
Fat mass	-3.80±0.47	-4.29±0.47	0.462
Fat percentage	-2.20±0.42	-2.47±0.42	0.652
WHR	-0.02±0.02	-0.02±0.02	0.944

SBP	-9.1±1.9	-8.9±1.9	0.918
DBP	-8.4±1.2	-8.2±1.2	0.970
Mean heart rate	0.7±1.2	2.1±1.2	0.374
WBC	-19.5±16.0	-5±15.9	0.283
hs-CRP	-0.60±0.18	-0.49±0.18	0.673
Glucose (mmol/l)	-0.40±0.09	-0.20±0.09	0.122
Insulin	-1.96±0.50	-1.77±0.49	0.797
HOMA-IR	-0.60±0.15	-0.60±0.15	0.993
Back pain, VAS score	-1.07±0.22	-0.60±0.22	0.238
Total calorie intake	-494.5 ± 66.7	-370.1 ± 63.6	0.181

Figures 2A and 2B show the adjusted mean changes of concentrates of lipids and FMD. Changes in TC and non-HDL-C were significantly greater in the orlistat/phentermine group than the placebo/phentermine group (-0.62±0.07 mmol/l vs. -0.32±0.07 mmol/l, respectively, p=0.005; -0.53±0.07 mmol/l vs. -0.30±0.07 mmol/l respectively, p=0.016). Although there was no statistical significance, adjusted mean LDL was further decreased in the orlistat/phentermine group than in the placebo/phentermine group (0.36±0.05 mmol/l vs -0.21±0.06 mmol/l, p=0.053). Adjusted mean changes in TG were not significantly different between groups.

Adjusted mean changes in endothelium-dependent FMD were significantly greater in the orlistat/phentermine than in the placebo/phentermine group (4.97±0.98% vs. 2.05±0.99%, respectively; p=0.038), while the changes in endothelium-independent NMD were not significantly different.

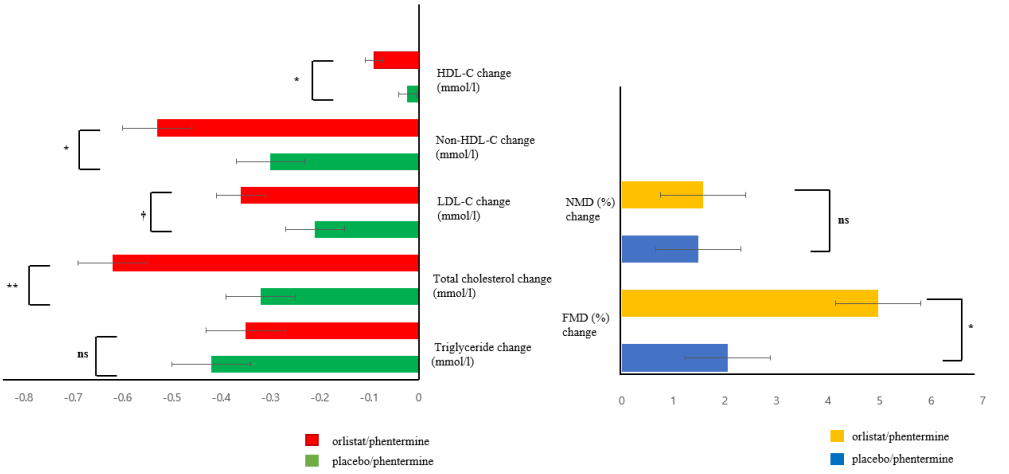


Figure 2. Adjusted mean changes of lipids and flow mediated dilatation (FMD)
HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; FMD, flow mediated dilatation; NMD, nitroglycerin mediated dilatation
(A): Lipid profile (B): endothelium dependent FMD and endothelium independent NMD

** p <0.01, * p <0.05, †p <0.1, ns: non-significance

The changes of lipids, FMD, and NMD were similar in the per protocol set (n=96) (Appendix Table 1).

Appendix Figure 1 shows a spider plot displaying standardized changes of lipids (TC, TG, non-HDL, LDL, and HDL), FMD, and NMD. Changes of FMD were more prominent in the orlistat /phentermine group. Changes of TC, non-HDL, LDL and HDL were also more prominent in the orlistat/phentermine group.

One volunteer was incidentally diagnosed with atrial septal defect during screening and was unable to participate in the study. There were no other findings on transthoracic

echocardiography (TTE) and no cases of increased right ventricular systolic pressure. In both groups, LV, diastolic function measured by E/E ratio was significantly improved (Appendix Table 2) with no significant difference between groups.

Adverse event

The percentages of patients with adverse event in the full analysis set were similar between the placebo/phentermine group (n=18 [32.1%]) and the orlistat/phentermine group (n=23 [40.4%]) (Table 6). The most common adverse event reported in the placebo/phentermine group was insomnia (12.5%), followed by dry mouth (7.1%) and depressive mood (3.6%) and heart palpitation (3.6%). Other infrequently reported AEs for this group were constipation, headache and impotence (1.8% each). The most common adverse events reported in the orlistat/phentermine group were insomnia (8.8%) and steatorrhea (8.8%) followed by constipation (5.3%), nervousness (3.5%) and diarrhea (3.5%). Depressive mood, nausea, dry mouth, dizziness, headaches and impotence were each reported once (1.8% each) for this group.

Table 6. Adverse events of placebo/phentermine and orlistat/phentermine groups

	Total (112)	Placebo/phentermine (55)	Orlistat/phentermine (57)	P-value
Adverse events, n (%)	41(36.3)	18 (32.1)	23 (40.4)	0.364
Insomnia	12 (10.6)	7 (12.5)	5 (8.8)	0.520
Steatorrhea	5 (4.4)	0	5 (8.8)	0.023
Constipation	4 (3.5)	1 (1.8)	3 (5.3)	0.317

Dry mouth	5 (4.4)	4 (7.1)	1 (1.8)	0.156
Nervousness	2 (1.8)	0	2 (3.5)	0.083
Depressive mood	3 (2.7)	2 (3.6)	1 (1.8)	0.548
Nausea	1 (0.9)	0	1 (1.8)	0.311
Diarrhea	2 (1.8)	0	2 (3.5)	0.157
Palpitations	2 (1.7)	2 (3.6)	0	0.150
Dizziness	1 (0.9)	0	1 (1.8)	0.311
Headache	2 (1.8)	1 (1.8)	1 (1.8)	0.891
Impotence	2 (1.8)	1 (1.8)	1 (1.8)	0.891

Adverse events reported in the orlistat/phentermine group were more frequently related to GI tract disturbances (steatorrhea). Adverse events related with phentermine were similar between groups, transiently occurred, and were mostly mild to moderate in severity.

Safety were measured by BP, heart rate, and echocardiography. Compared with baseline, both SBP and DBP decreased by about 10 mmHg at 12 weeks, in both groups. Echocardiography revealed no valvular heart diseases, pulmonary artery hypertension, or other significant findings.

Lower back pain

We recruited patients who were overweight or obese with lower back pain with a VAS score over 3.

The baseline median IQR of the VAS score and mean ± SD of the ODI were not significantly different between groups. The average VAS improved from baseline to 12 weeks by 1 point in the orlistat/phentermine group ($p=0.005$) and 2 points ($p<0.001$) in

the placebo/phentermine group.

The ODI was also significantly improved from baseline to 12 weeks by 3 point in the orlistat/phentermine group (p=0.012) and 5 point in placebo/phentermine group (p=0.002). The differences in the VAS and ODI scores were not significantly different between groups.

IV. DISCUSSION

During this study, mean weight loss was decreased by about 7.8% in both groups, which indicates concomitant treatment of orlistat with phentermine does not provide additive weight loss effects. Our findings are similar to previous studies which report weight loss in orlistat plus sibutramine was similar to sibutramine alone.[42,43] However, unlike previous studies which focused on weight loss as a primary endpoint, we investigated the effect of concomitant orlistat and phentermine on endothelial cell function. Our results, measured by FMD, indicate that orlistat plus phentermine, along with mild exercise and calorie reduction, results in greater improvement in endothelial cell function in overweight and obese adults than phentermine alone.

In the current study, mean weight loss was similar between groups. Moreover, BMI, WC, BP, CRP, and insulin levels were significantly improved, and the adjusted mean changes were similar between groups. We believe that these metabolic parameters were mainly affected by weight loss.

We found that HDL-C significantly decreased in the orlistat/phentermine group. Although the exact reason for decrease of HDL in orlistat/phentermine is not clear, due

to its mechanism of orlistat inhibits an intestinal fat digestion and absorption about 30% of the dietary fat, HDL-C simultaneously decreased with decreasing serum cholesterol.[44] However, several studies reported that , after at least 6months, the HDL-C subsequently increased with sustained long-term weight loss.[44,45] Because this study was conducted during relatively short term period (12weeks), it was difficult to predict continuous changes in HDL-C.

Additionally, we included overweight or obese adults with lower back pain with a more than VAS score over 3. Physical limitations with lower back pain could be important obstacle for reduction weight.[18] We found that positive role of weight loss in improvement in pain score and quality score related to lower back pain. Actually, recent studies have suggested that overweight/obesity could aggravate the lower back pain.[17]

Many anti-obesity drugs failed to enter the market and several were withdrawn due to safety concerns some of which were related to CVD risk (including valvular heart disease, pulmonary hypertension, stroke, and other cardiovascular-related increased mortality). Therefore, the FDA requires that anti-obesity drugs must meet the following criteria: (a) mean placebo-subtracted weight loss ≥5% or (b) proportion of drug-treated subjects who lose ≥5% of baseline body weight is ≥35% and (c) approximately double the proportion who lose ≥5% in the placebo/phentermine group.[46] Additionally, the FDA require anti-obesity drugs to result in improvements in BP, heart rate, lipid profile, glucose, insulin, WC, and quality of life.[46] Although phentermine is a widely prescribed anti-obesity drug in the US and other countries, including Korea,[26,27] there have been reports of potential safety concerns including elevated heart rate and increased BP,

stroke,[47] vasoconstriction,[48] mental illness[49] and pulmonary arterial hypertension.[50] Therefore, phentermine is contraindicated in patients with progressive atherosclerosis, valvular heart disease, symptomatic CVD, pulmonary hypertension, and uncontrolled hypertension.

The Korean Ministry of Food and Drug Safety investigated the prescription of appetite suppressants, from July 2018 to April 2019, to facilitate the development of a strategy to inform physicians about appropriately prescribing weight loss medications and providing safe and supportive environments to reduce the need for psychotropic drugs.[51] In Korea, 1.16 million patients were prescribed appetite suppressants during a 10 month period. This accounts for one out of 45 Koreans (2.2 percent of the population). Of note, the largest number of patients (740,000 people) were prescribed phentermine.[51] This strongly suggests that strategies are needed to prevent and monitor the appetite suppressants for cardiovascular adverse events in line with growing prevalence of obesity.

Orlistat, is long-term approved anti-obesity drug and the only drug indicated by the US FDA for use in adolescents aged 12 years and older.[21] Orlistat also has no reported significant interactions with other anti-obesity drugs, including phentermine[52,53] and no serious adverse event related to its use in combination with norepinephrine and or a serotonin-reuptake inhibitor.[42,43]

In this study, endothelium-dependent FMD was significantly improved in the orlistat/phentermine group only. The NMD was not significantly affected in either group. Several studies have investigated the role of orlistat in endothelial cell function.

Sekuri et al[54] showed orlistat treatment for 12 weeks improved FMD in young obese women (age 18-34 years). Brook et al [55] found no significant improvement in FMD after 12 weeks open-label trials in healthy overweight adults (age 18-50 years). The participants in these two studies were relatively healthy obese adults. Our study included not only obese adults but also overweight adults with comorbidities such as diabetes, hypertension and dyslipidemia. Liu.J et al[32] reported a significant positive effect of orlistat on FMD in obese adults with hypertension. However, this study did not have a control group, and neither did the studies by Sekuri and Brook. A randomized controlled trial[13] showed orlistat treatment improved endothelium dependent vasodilatation in obese women with gestational diabetes, despite similar weight loss in the orlistat and placebo group. Bergholm et al[13] suggests that blood flow response to acetylcholine is significantly associated with LDL-C reduction by orlistat, not with weight reduction. Muls et al[41] also showed that orlistat reduces TC and LDL-C in overweight and obese patients with hypercholesterolemia, independent of weight loss. These results are in line with our own findings. The current study demonstrated that TG, TC, non-HDL-C, and LDL-C were significantly decreased in both groups over the 12-week treatment period. Despite identical weight loss between groups, we found that the orlistat/phentermine group had greater reduction of total cholesterol and non-HDL, and a mild, but greater reduction of LDL cholesterol compared to the placebo/phentermine. These results could support that reduction of serum cholesterol might lead to the improvement of endothelial cell function in this study.

Feron et al[56] demonstrated that hypercholesterolemia decreases NO production in the

endothelium by upregulating the caveolin protein and inhibiting eNOS activity. Therefore, in hypercholesterolemia, the reduced bioavailability of NO leads to impaired endothelium-dependent vasodilation.[57] Previous studies have demonstrated that statin, a class of cholesterol lowering drugs, improved endothelial function by increasing NO bioavailability.[58,59]

Anti-inflammatory and anti-cancer effects of orlistat could be another possible mechanisms to support oust results.[34,35,60] Inflammation is a key factor in pathophysiology in obesity and CVD.[61] Inflammation has been known to decrease endothelial cell function by decreasing NO availability through labilizing eNOS mRNA expression.[62] Samuelsson et al[63] reported that treatment with orlistat for 1year significantly reduced the tumor necrosis factor alpha (TNF-alpha), a potent inflammatory mediator compared to placebo. Although there were not significant differences in reduction of CRP in both groups in our study, these results might be attribute to short-term orlistat treatment duration.

Previous study revealed that elevated free fatty acids (FFA) is related with impaired endothelial cell function.[64] First, FFA reduced NO production in endothelial cell by down-regulation the AMPK/PI3K/Akt/eNOS signaling.[65] Second, FFA also induced the endothelial cell dysfunction through disruption of calcium signaling mediated NO production.[66] Third, FFA, per se, is a source of reactive oxygen species which lead to oxidative stress that impair the endothelium.[67] Interestingly, orlistat has been known as a novel fatty acid synthase inhibitor.[34,35] Therefore, treatment with orlistat could lead to the improvement in endothelial functions and vasodilatation.

This is the first randomized double blinded placebo-controlled study to investigate the efficacy and safety of concomitant administration of orlistat and phentermine. However, there are some limitations in this study. First, FMD is the standard test for noninvasive assessment of conduit artery endothelial function because it is repeatable, validated, and has a firm link to biology characteristics.[6] However, FMD requires highly trained technicians and FMD could be affected by temperature and environmental factors. Second, the treatment term (12 weeks) is relatively too short to fully evaluate the effect of phentermine or orlistat on cardiovascular risk such as HR, as well as long-term safety evaluation. Third, this study included Korean subjects only, thus these results may not be transferrable to different ethnicities. Finally, although investigators instructed patients to decrease calorie intake by 500 kcal and preform light to moderate exercise more than twice a week, adherence to diet and exercise regimen was not mandatory. Nonetheless, participants consumed the reduced calorie about 500kcal and the proportion of exercise was increased about 13% in the both groups.

V. CONCLUSION

This study demonstrated that orlistat improves endothelial-dependent FMD in obese adults independent of weight loss. Adding orlistat to phentermine may be a practical approach in clinical practice to reduce cardiovascular risk by improving endothelial cell function, especially in overweight patients with comorbidities or obese patients who are physically restricted.

Appendix Table 1. Changes of lipids, flow mediated dilatation and nitroglycerin mediated dilatation from baseline to 12 weeks in placebo/phentermine and orlistat/ phentermine in per protocol set (n=96)

	Placebo/phentermine		**Orlistat/phentermine**		P-value†
Lipids	**Baseline**	**12 weeks**	**Baseline**	**12 weeks**	
Triglyceride	1.53	1.09	1.36	1.14	
	(1.03, 2.00)	(0.90, 1.36)*	(0.98, 1.67)	(0.83, 1.49)*	
Changes	-0.48 ± 0.08		-0.43 ± 0.08		0.657
Total cholesterol	5.27 ± 1.06	4.82 ± 0.94*	5.05 ± 0.94	4.39 ±0.71**	
Changes	-0.41 ± 0.08		-0.70 ± 0.76		0.009
LDL cholesterol	3.36 ± 0.8	3.05 ± 0.73*	3.08 ± 0.65	2.72 ± 0.55**	
Changes	-0.26 ± 0.06		-0.41 ± 0.06		0.071
HDL cholesterol	1.34 ± 0.24	1.32 ± 0.26	1.37 ± 0.35	1.26 ± 0.26**	
Changes	-0.03 ± 0.02		-0.10 ± 0.02		0.013
Endothelial cell function					
FMD (%)	11.6 ± 5.5	13.8 ± 6.6	10.6 ± 6.3	16.5 ± 8.3	
Changes	2.12 ± 1.19		6.02 ± 1.14		0.020
NMD (%)	12.7 ± 6.3	14.3 ± 6.0	11.0 ± 5.5	13.0 ± 6.3	
Changes	1.59 ± 1.07		2.27 ± 1.02		0.645

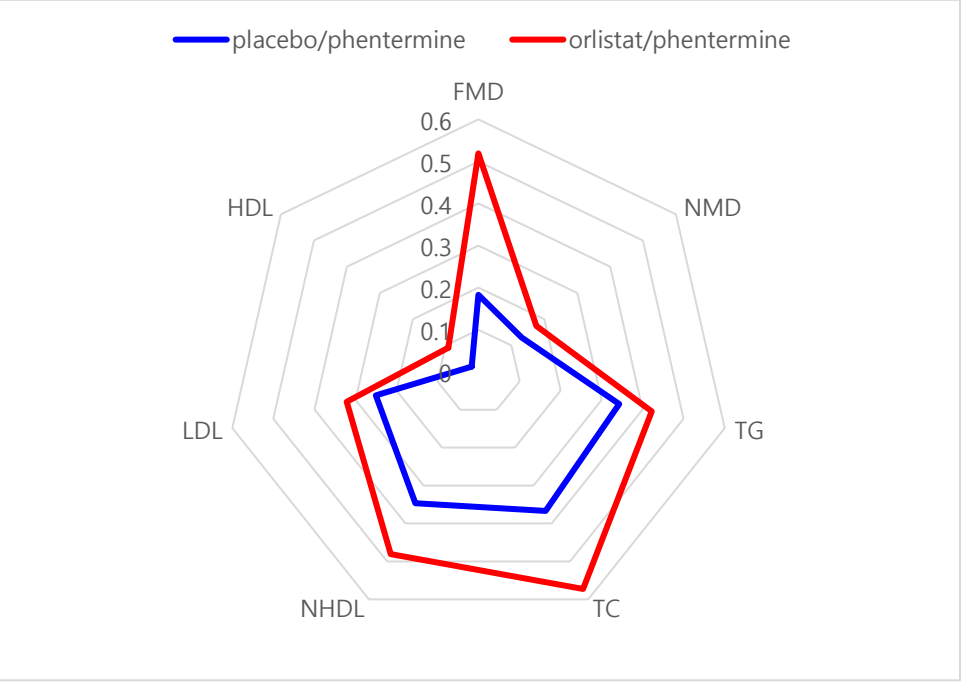
*p-values<0.05, **p-value <0.01

†p-value; differences of changes between two groups calculated using an analysis of covariance after adjusting for each baseline values.

Appendix Table 2. Characteristics of transthoracic echocardiography in placebo/phentermine and orlistat/phentermine groups at baseline and 12 weeks

	Placebo/phentermine		**Orlistat/phentermine**	
	Baseline	**12 weeks**	**Baseline**	**12 weeks**
LVEF, %	62.2 ± 4.7	63.0 ± 4.1	62.6 ± 5.8	62.3 ± 5.4
Changes	0.63 ±0.64		-0.11 ± 0.64	
E wave velocity, cm/s	0.52 ± 0.13	0.49 ± 0.13*	0.51 ± 0.14	0.48 ± 0.13*
Changes	-0.03 ± 0.01		-0.04 ± 0.01	
A wave velocity, cm/s	0.57 ± 0.11	0.56 ± 0.11	0.56 ± 0.12	0.54 ± 0.11
Changes	-0.02 ± 0.01		-0.02 ± 0.01	
E/A	0.86 (0.72, 1.14)	0.75 (0.61, 1.14)**	0.89 (0.71, 1.17)	0.71 (0.55, 1.67)**
Changes	-0.001 ±0.078		-0.112 ± 0.078	
E wave Decel time, ms	150 (150, 180)	150 (150, 179)	150 (150, 175)	150 (150, 176)
Changes	-2.23 ± 3.80		0.07 ± 3.79	
E’	0.06 (0.05, 0.08)	0.06 (0.05, 0.08)	0.06 (0.05, 0.07)	0.06 (0.05, 0.08)
Changes	0.001 ± 0.002		0.001 ± 0.002	
E/E’	8.32 ±1.74	7.76 ± 1.66**	8.22 ± 1.79	7.77 ± 2.10*
Changes	-0.54 ± 0.21		-0.47 ± 0.21	
LAVI	16.7 ± 4.2	16.1 ± 4.8	18.2 ± 4.9	16.6 ± 3.9**
Changes	-0.84 ± 0.44		-1.33 ± 0.36	
LVEDD, mm	45.7 ± 3.7	45.2 ± 3.9	45.8 ± 3.9	44.8 ± 4.1*
Changes	-0.51 ± 0.37		-0.96 ± 0.36	
LVESD, mm	31.5 ± 2.9	31.0 ± 3.0	31.4 ± 3.1	30.9 ± 3.3
Changes	-0.48 ± 0.27		-0.52 ± 0.26	
RVSP	26.2 ± 4.3	25.6 ± 4.1	26.2 ± 3.1	25.3 ± 3.0
Changes	-0.61 ± 0.44		-0.92 ± 0.44	

* P value <0.05



Appendix Figure 1. Spider plot of changes of lipids, flow mediated dilatation, and nitrogen mediated dilatation

FMD, flow mediated dilatation; NMD, nitrogen mediated dilatation; TG, triglyceride; TC, total cholesterol; NHDL, non-high density lipoprotein; LDL, low density lipoprotein; HDL, high density lipoprotein

Blue line, placebo/phentermine; Red line, orlistat /phentermine

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ABSTRACT (IN KOREAN)

Orlistat 와 phentermine 병용요법이 위약과 phentermine 단독 요법에 비해 비만 및 과체중 환자들의 혈관 내피세포 기능에 미치는 영향: 무작위, 이중 맹검, 위약 대조군 연구

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권유진

배경: 비만은 심혈관계 질환의 중요한 위험인자이다. 비만은 혈관 내피세포 기능을 악화시킨다고 알려져 있다. 혈관 내피세포 기능 이상은 관상동맥질환의 선행 인자인 혈관 손상의 초기 지표이다. 체중 감소는 심혈관계 질환의 위험을 줄일 수 있는 중요한 치료 전략 중 하나이나, 몇몇의 중추 신경에 작용하는 항비만 약제는 심혈관계에 대한 부작용 때문에 주의가 요구된다. 오르리스타트는 장에 작용하는 지방흡수 억제제로서 식이 지방의 약 30% 정도의 흡수를 저해함으로써, 비만 환자에서 혈압 및 혈당을 비롯하여 혈청 콜레스테롤 수치와 같은 심혈관계 관련 대사적 지표를 개선하는 것으로 알려져 있다. 본 연구는 오르리스타트와 펜터민을 병용하였을 때 펜터민을 단독 사용하였을 때와 비교하여 과체중 및 비만 환자에서 혈관 내피세포 기능 개선 정도를 알아보고자 하였다.

방법: 본 연구는 12주 동안 무작위 이중 맹검 위약 대조군 연구로 진행이 되었다. 총 114명의 허리 통증이 있으면서 동반질환이 있고 체질량지수가 27kg/m2 이상인 과체중 환자 또는 허리 통증이 있으면서 체질량지수 30kg/m2 이상인 비만 환자가 본 연구에 등록되었다. 1:1 무작위 배정이 되었으며, 실험 군은 오르리 스타트 120mg 하루 세 번과 펜터민 37.5mg을 하루 한 번 처방을 받았고, 대조군은 위약 하루 세 번과 펜터민 37.5mg을 하루 한 번 처방을 받았다. 두 군 모두 에너지 섭취량을 하루에 약 500kcal 줄이고 경증에서 중등도의 운동을 일주일에 세 번 이상 하도록 권고받았다. 본 연구의 일차적 목표는 초음파로 측정한 혈관 내피세포 확장 정도였다. 본 연구의 이차적 목표는 체중, 체질량지수, 그리고 대사적 지표의 변화를 살펴보는 것이었다. 본 연구의 분석은 연구에 등록된 후 스크리닝 검사를 받고, 약품을 한 번이라도 처방을 받은 사람은 모두 분석 대상자로 하였다.

결과: 12주 동안 오르리스타트와 펜터민 병용 군과 위약과 펜터민 병용 군의 평균 체중은 각각 6.1kg 와 6.0kg 유의하게 감소하였으나 두 군 사이의 차이는 없었다. 혈관 내피세포의 존 기능 평가에서 오르리 스타트와 펜터민 병용 군에서 혈관 확장 정도의 초깃값을 보정한 뒤 위약과 펜터민 병용 군보다 더 유의한 혈관 내피세포의 존 확장을 보였다. 혈관 내피세포 비 의존 기능 평가에서는 양 군의 혈관확장 정도는 유의하지 않았으며, 양 군 간의 유의한 차이는 없었다. 오르리 스타트와 펜터민 병용 군에서 총 콜레스테롤과 비 HDL 콜레스테롤은 각 초기값을 보정한 뒤에 위약과 펜터민 병용 군보다 더 유의하게 감소하였다.

결론: 오르리스타트와 펜터민을 병용한 군에서 위약과 펜터민 병용군에 비해 유의한 혈관 내피세포 기능 개선을 보였다. 비만하거나 동반질환이 있으면서 과체중인 환자에서 오르리 스타트를 펜터민에 병용하여 치료하였을 때 심혈관계 위험을 개선할 수 있다.

핵심되는 말: 오르리스타트; 펜터민; 비만; 허리통증; 콜레스테롤; 혈관내피세포