Orlistat Plus Low Caloric Diet Improves Cardiovascular Risk Factors and Cardiac Functions Assessed By Tissue Doppler Echocardiography in Obese Women

Obez Kadınlarda Orlistat Artı Düşük Kalorili Diyet Kardiyovasküler Risk Faktörlerini ve Doku Doppler Ekokardiyografiyle Belirlenen Kalp Fonksiyonlarını İyileştirir

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ABSTRACT Objective: Investigating the effect of orlistat plus low calorie diet on echocardiographic, physical and biochemical parameters in obese female patients. **Material and Methods:** A total of 54 women (with a mean age of 42 ± 9 years) with body mass index (BMI) ≥ 30 kg/m^2 and without history of hypertension, diabetes mellitus and any cardiac disease comprised the sample of the study. All participants used orlistat and low caloric diet combination and were followed-up for one-year. Physical, biochemical and echocardiographic variables were measured at baseline and at the end of month one, month six and year one. **Results:** Five patients were dropped out and the remaining 49 were analyzed. BMI of the study population was significantly reduced at the end of one year (33.2 ± 3.4 vs 30.7 ± 3). All investigated physical and biochemical parameters except waist hip ratio, diastolic blood pressure and heart rate improved significantly at the end of the study. Although, there were no significant improvements in left ventricular geometrical and mitral inflow parameters, the tissue Doppler parameters significantly improved at the end of the study. **Conclusion:** This study showed that orlistat in combination with low caloric diet improved physical, biochemical and left ventricular tissue Doppler echocardiographic parameters in obese women. We conclude that management of obesity by using orlistat and low caloric diet reduces cardiovascular risk factors and improves cardiac functions.

Key Words: Anti-obesity agents, orlistat, echocardiography

ÖZET Amaç: Obez kadınlarda orlistat ve düşük kalorili diyet tedavisinin ekokardiyografik, fiziksel ve biyokimyasal parametreler üzerindeki etkisini araştırmaktır. **Gereç ve Yöntemler:** Ekzojen obezite tanısı almış, beden kitle indeksi (BKİ) ≥ 30 kg/m^2 olan, hipertansiyon, diabetes mellitus ve herhangi bir kardiyak hastalık öyküsü olmayan toplam 54 hasta (ortalama yaşları 42 ± 9 yıl olan) çalışmanın örneklemini oluşturdu. Tüm katılımcılar orlistat ve düşük kalorili diyet tedavisi kullandılar ve bir yıl süreyle takip edildiler. Çalışmanın başlangıcında, 1. ay, 6. ay ve 1. yıl sonunda fiziksel, biyokimyasal ve ekokardiyografik değişkenlere ilişkin ölçümler yapıldı. **Bulgular:** Çalışma süresince 5 olgu çeşitli nedenlerle çalışmadan çıkarıldı ve kalan 49 olgunun verileri değerlendirmeye alındı. Bir yılın sonunda çalışma grubunun BKİ'de anlamlı bir azalma (33.2 ± 3.4'e karşın 30.7 ± 3) vardı. Çalışmanın sonunda, bel kalça oranı, diyastolik kan basıncı ve kalp hızı dışında değerlendirilen tüm fiziksel ve biyokimyasal parametrelerde anlamlı bir iyileşme gözlendi. Sol ventrikül geometrik ve mitral içe akım kayıtlarında anlamlı bir değişiklik olmamasına rağmen, çalışma sonunda doku Doppler parametrelerinde anlamlı bir iyileşme vardı. **Sonuç:** Bu çalışma, orlistat ile düşük kalorili diyet kombinasyonunun, obez kadınlarda fiziksel, biyokimyasal ve doku Doppler ekokardiyografi parametrelerinde anlamlı bir iyileşme sağladığını göstermektedir. Orlistat ve düşük kalorili diyet ile obezite tedavisinin kardiyovasküler risk faktörlerini azalttığı ve kalp fonksiyonlarını iyileştirdiğini düşünüyoruz.

Anahtar Kelimeler: Anti-obezite Ajanları, orlistat, ekokardiyografi

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Obesity is among the major health problems in industrialized countries as well as in the developing world.[1,2] Excess caloric intake and reduced physical activity are the main causes of obesity. According to the 1997 WHO report, obesity related health problems could be attenuated with effective treatment.[1] Obesity and obesity-related major cardiac risk factors such as hypertension, diabetes mellitus and dyslipidemia pose major threats to public health especially for women.[3-5] Therefore, there is an ever-increasing interest in the treatment of obesity with both pharmacologic and non-pharmacologic approaches. Orlistat is a drug that improves weight control. It inhibits pancreatic lipase in the gastrointestinal tract and prevents the absorption of approximately 30% of dietary fat.[6,7]

Interestingly, there is also a paucity of data about the effect of weight loss induced by orlistat plus low calorie diet on cardiac functions despite relatively widespread use of the drug. In this study, we aimed to investigate the effect of orlistat plus low caloric diet therapy on physical, biochemical and echocardiographic parameters in obese females.

MATERIAL AND METHODS

Fifty-four obese female subjects without history of hypertension, diabetes mellitus, acute or chronic renal disease, acute or chronic hepatic disease, acute or chronic thyroid disease, Cushing disease and coronary artery disease, with a mean age of 33.2 ± 3.4 years were enrolled in the study. Five patients were dropped-out because of drug intolerance (gastrointestinal side effects) during the follow-up period, and the data of the remaining 49 were analyzed. Obesity was defined as having a BMI over 30 kg/m^2. The study protocol was reviewed and was approved by the local ethics committee and all participants were informed about the study protocol and provided informed consent.

All patients were weighed on calibrated scales with only their underclothes on and BMI were calculated. Waist circumference was measured in standing position at the middle of exhalation, from the line in the middle of the iliac protrusion. Hip circumference was measured from the most significant point of the iliac protrusion, crista iliaca anterior superior. Blood pressure was measured with a mercury sphygmomanometer following a 10 minutes rest Cigarette, tea and coffee abstinence was maintained at least for 30 minutes before these measurements.

Blood samples were obtained from the antecubital brachial vein after 10–12 h of fasting Plasma was separated by centrifugation and was analyzed immediately. A biochemical profile was obtained by automatic analyzer (R-A 1000, RA-XT autoanalyzer, Technicon, Tarrytown, NY). A Coulter MD II device /Coulter MD II Series Analyzer, Coulter Cooperation, Miami, FL, USA) was used for complete blood count analysis.

Echocardiographic evaluation was performed at baseline and at the end of the study by using a 2.5-MHz sector probe with Vingmed System V (GE, Horten, Norway) machine capable of tissue Doppler imaging. Left ventricular dimensions were measured in parasternal long axis with M-mode and ejection fraction was calculated according to Teichholz formula. We used Doppler echocardiography for both mitral inflow (peak E wave velocity, peak A wave velocity, E wave deceleration time, E/A ratio) and aortic flow measurements (peak aortic wave velocity, aortic ejection time).

Color tissue Doppler imaging (TDI) was used for obtaining samples from both mitral (septal and lateral in apical four chamber view) and tricuspid annulus (apical four chamber view). Necessary adjustments were made on machine for obtaining the best signal to noise ratio. The incident angle between the interrogating Doppler beam and longitudinal motion of the ventricle was kept as small as possible.[8]

Color TDI data were analyzed off-line with the Echopac software (GE Vingmed) provided with the machine. The following parameters were measured by tissue Doppler; mitral and tricuspid recordings: peak early diastolic myocardial tissue velocity (Ea), Ea-wave deceleration time, peak late diastolic

myocardial tissue velocity (Aa), Ea/Aa ratio, peak systolic myocardial tissue velocity (Sa).[9] Measurements were performed in 3 cardiac cycles and the average value was calculated for subsequent analyses.

After this initial evaluation every patient was encouraged to follow a diet prepared by a hospital dietician in which total calorie intake was decreased by 20% (fat-related calorie <30% of total calorie). In addition, allsubjects were prescribed 120 mg Orlistat, t.i.d. (Xenical 120 mg®, Hoffmann-La Roche). Follow-up period was one year during which three visits were performed at 1, 6 and 12 months.

Continuous variables were expressed as mean ± standard deviation and categorical variables were expressed as numbers and percentages. Two-tailed student's *t* test and Wilcoxon sign tests were used to compare continuous and categorical variables between groups, respectively. For continuous variables, Wilcoxon sign test was used if the normality test results, which were tested by Kolmogrow–Smirnow test, did not show normally distributed data. Statistical difference was defined by a p value below 0.05.

Intraobserver variability was assessed in ten patients by repeating the measurements on two occasions. To test the interobserver variability, a second observer who was blinded to the results of the first examination repeated the measurements. Variability was calculated as mean percent error, derived as the difference between the two sets of measurements, divided by the mean value of the observations.

RESULTS

At the end of the study, all anthropometric and biochemical parameters except waist/hip ratio, high-density lipoprotein cholesterol, diastolic blood pressure and heart rate demonstrated statistically significant improvement with orlistat plus low caloric diet therapy compared to baseline (Table 1). By the end of the study, mean BMI of the study population had significantly decreased from 33.2 ± 3.4 to 30.7 ± 3 kg/m^2 (p< 0.01).

The majority of the patients (88% n= 43) had stage 1 diastolic dysfunction at baseline and only two had stage 2 diastolic dysfunction (n= 2, 4%) (normal E/A ratio in mitral inflow but a ratio lower than 1 in Color TDI). Wall thickness and left ventricular systolic function were all within normal limits initially. We did not find any significant improvement in diastolic functions with orlistat therapy. However, mitral lateral Sa and Aa waves, mitral septal Sa, Ea and Aa waves and tricuspid Sa wave velocities increased significantly (Table 2).

TABLE 1: Anthropometric and biochemical parameters during follow-up.

Parameters	Baseline	1st month	6th months	12th months	p value
Waist/hip ratio	0.87 ± 0.05	0.86 ± 0.034	0.85 ± 0.03	0.86 ± 0.03	0.215
Waist circ. (cm)	110.8 ± 7.2	108.4 ± 7.2	101.1 ± 7.3	104.5 ± 6.6	0.008
Hip circ. (cm)	128.4 ± 9	125.7 ± 9	123.1 ± 8.8	120.7 ± 8.5	0.006
Total C (mg/dL)	183.7 ± 41.8	163 ± 43	150.8 ± 29	150.2 ± 29	<0.001
LDL-C (mg/dL)	165.9 ± 23.2	154 ± 32	138 ± 22.3	135.4 ± 20.7	<0.001
*HDL-C (mg/dL)	43 ± 35	42 ± 29.1	42.8 ± 23	37.9 ± 24.1	0.034
Triglyceride (mg/dL)	168.8 ± 33.6	156.2 ± 38.1	134.9 ± 35.3	139.7 ± 27.7	0.009
FBG (mg/dL)	125.7 ± 24.8	114 ± 27.1	112.4 ± 24.5	110.3 ± 15.6	0.007
Systolic BP (mmHg)	137 ± 19	136.8 ± 15.3	132.8 ± 14.8	132.6 ± 15.2	0.042
Diastolic BP (mmHg)	83.25 ± 15.7	81.3 ± 11.8	75.8 ± 11.7	78.8 ± 10.1	0.180
Heart rate (beat/min.)	83.6 ± 15.8	82.6 ± 11.8	79.8 ± 10.31	81.6 ± 9.8	0.084
Weight (kg)	89.9 ± 9.4	86.9 ± 8.8	85.3 ± 8.8	83.8 ± 8.3	0.003
BMI	33.2 ± 3.4	31.9 ± 3.2	31.3 ± 3.2	30.7 ± 3	0.009

p values represent the comparison between baseline and month 12 values. FBG: Fasting blood glucose; BMI: Body mass index; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein-cholesterol; BP: Blood pressure. * not normally distributed data.

TABLE 2: Echocardiographic parameters and their statistical comparison.

Parameters	Baseline	12th months	p value
IVSd	10 ± 1.7	9.8 ± 1.5	0.215
LVPWd	10.2 ± 1.5	9.9 ± 1.4	0.371
LVIDd	46.9 ± 6.5	47.4 ± 5.4	0.104
EF	63.1 ± 5.9	64.3 ± 5.4	0.151
FS	34.4 ± 5.0	35.6 ± 4.2	0.725
Mitral E velocity (m/sec)	0.69 ± 0.2	0.69 ± 0.1	0.850
*Mitral A velocity (m/sec)	0.96 ± 0.30	0.95 ± 0.25	0.618
*Mitral E/A ratio	0.75 ± 0.30	0.77 ± 0.25	0.110
Mitral E wave deceleration time (ms)	226.80 ± 55.9	217.85 ± 38.79	0.761
Aortic velocity (m/sec)	1.09 ± 0.22	1.15 ± 0.23	0.031
Aortic ejection time (milliseconds)	298 ± 18.4	275 ± 19.8	0.082
*Mitral lateral tissue Doppler S velocity (m/sec)	9.40 ± 2.12	9.90 ± 2.09	0.036
*Mitral lateral tissue Doppler E velocity (m/sec)	8.93 ± 2.88	9.53 ± 3.22	0.121
Mitral lateral tissue Doppler A velocity (m/sec)	11.48 ± 2.63	12.37 ± 2.74	0.009
*Mitral septal tissue Doppler S velocity (m/sec)	5.94 ± 2.28	7.67 ± 1.71	<0.001
*Mitral septal tissue Doppler E velocity (m/sec)	7.12 ± 2.2	7.90 ± 2.53	0.024
*Mitral septal tissue Doppler A velocity (m/sec)	9.78 ± 2.63	10.54 ± 3.23	0.005
Tricuspid lateral tissue Doppler S velocity (m/sec)	14.88 ± 3.08	15.89 ± 2.72	0.027
Tricuspid lateral tissue Doppler E velocity (m/sec)	11.75 ± 2.81	12.12 ± 3.08	0.241
*Tricuspid lateral tissue Doppler A velocity (m/sec)	16.28 ± 5.4	16.57 ± 5.66	0.654

IVSd: Interventricular septal thickness (diastolic); LVPWd: Left ventricular posterior wall thickness (diastolic), LVIDd: Left ventricular internal diameter (diastolic), EF: Ejection fraction; FS: Fractional shortening. * not normally distributed data.

Intraobserver and interobserver variability for measurements derived from TDI analysis of mitral annulus motion (S, E and A) and Doppler-derived parameters (E, A) ranged from 1.3%-7.4%, respectively.

Intraobserver and interobserver variability for measurements derived from TDI analysis of tricuspid basal-lateral wall motion (S, E and A) and Doppler-derived parameters (E, A) ranged from 4.6 %-8.8 %, respectively.

DISCUSSION

This study showed that orlistat in combination with decreased caloric diet improved physical, biochemical and left ventricular tissue Doppler echocardiographic parameters in obese women.

Beneficial effects of moderate weight loss on cardiovascular system were shown by various studies; however, losing weight only with diet or maintaining the same weight can be difficult.[10,11] Therefore, concomitant medical treatment for obesity is also a recommended approach. Although sibutramine and orlistat are the two most-studied drugs, controlled studies have established that orlistat 120 mg, t.i.d. for 1 year, in conjunction with a hypocaloric diet, enables weight reduction of 7.9 to 10.2% in non-diabetic obese individuals. The weight reduction of 6.2% in our study in obese female patients during the 1-year follow-up is consistent with the literature.[12,13]

Obesity in young otherwise-healthy women is associated with concentric left ventricular (LV) remodeling probably caused by metabolic disturbances (insulin resistance, increased free fatty acid levels, and increased levels of adipokines), activation of the renin-angiotensin-aldosterone and sympathetic nervous system, as well as elevated blood pressure in obese subjects, and decreased systolic and diastolic functions.[14-17] These early abnormalities in LV structure and function may have important implications for explaining the myocardial dysfunction that is associated with increased cardiovascular morbidity and mortality caused by obesity.[18,19] We observed a slight reduction in cardiac wall thickness with orlistat plus low calorie diet, which is consistent with the data of previous studies.[20-24]

The majority of our patients had diastolic dysfunction as reflected by reversed E/A ratio. Diastolic dysfunction was reported to be an indicator of early involvement of the myocardium in obesity and this clinical entity is reversible.[25-29] Although the improvement in mitral inflow E/A ratio with orlistat plus diet approach was not significant in our study, significant increases were detected in many color-TDI parameters. This discrepancy may be explained by the highly sensitive nature of the TDI method. Besides, mitral inflow parameters are affected by preload; however, TDI is relatively load-independent.[30-33] Indeed, TDI has been proposed as a more sensitive method for detecting changes in myocardial properties in various disease states. Therefore, our results, which showed significant changes in only TDI versus mitral inflow parameters, can be explained on this basis. Previous studies reported that myocardial performance index improved with the use of orlistat.[28] Although not reaching to statistical significance, ejection fraction improved by losing weight with the use of orlistat and low caloric diet (Table 2).

Orlistat plus low calorie diet changed our patients' lipid profile in a favorable way, which may be beneficial in terms of cardiovascular risk factors.[34-36] These changes in lipid profile may be attributed to orlistat's lipid lowering effect via inhibition of 30% of lipid absorption. The improvement in physical parameters (waist and hip circumference) may be associated with decrease in insulin resistance.[37] Previous studies were also consistent with our findings.[38]

Lifestyle changes are not only cost effective, but may be the best approach for individuals who desire to lose weight or to maintain their weight. The addition of drug therapy is also a possibility. Various pharmacological therapy interventions are available for the patient on a short or long-term basis.

In conclusion, management of obesity by using orlistat and low caloric diet improves obesity related cardiovascular risk factors and cardiac functions assessed by tissue Doppler echocardiographic parameters.

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