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The effect of orlistat treatment on cardiovascular novel inflammatory biomarkers

Zafer Yalim[1], Sumeyra Alan Yalim[2]

[1]Afyonkarahisar Health Sciences University, Faculty of Medicine, Department of Cardiology, Afyonkarahisar, Turkey
[2]Afyonkarahisar State Hospital, Department of Internal Medicine,Afyonkarahisar, Turkey

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Abstract

Increase in prevalence of obesity has become a worldwide major health problem. In general, greater body mass index (BMI) is associated with increased rate of death. New inflammatory markers (such as monocyte-to-HDL ratio (MHR), and cardiac risk ratio (CRR)) have been used as biomarkers of pathogenic inflammation and prognostication in multiple areas of medicine. Although they have been tested in many different diseases and conditions, how they have been affected in patients receiving orlistat therapy due to obesity has never been evaluated before. In this retrospective study, 197 patients who received orlistat treatment for the first time were included in the study were enrolled. All data (such as demographic profile, lipid profile, hs-CRP, hemogram, and biochemical parameters) of patients before the treatment and at the 3rd-month control after orlistat treatment were recorded. The gender ratios of the patients were male (%46.7) and female (%53.3) and mean age of patients was 47.13±10.9 years. In the comparison of patients before and after treatment, BMI was significantly decreased and the mean change was 3.4054 ($p<0.001$). Significant decrease in neutrophil (5.71±1.9, 5.39±1.5, $p=0.016$), monocyte (0.572±0.207, 0.508±0.164, $p<0.001$), and platelets (309.09±102.1, 276.08±60.2, $p=0.023$) were observed in blood cells. When the inflammatory parameters were examined, a significant decrease in hs-CRP (0.88±0.52, 0.67±0.28, $p<0.001$), in CRR (4.32±1.07, 3.94±0.92, $p<0.001$), in MHR (0.0135±0.0057, 0.0116±0.0049, $p<0.001$) were observed (before and after orlistat treatment, respectively). Also, significant improvement was observed in the lipid profile of the patients after orlistat treatment (for all values, $p<0.05$). In our study, we observed that inflammatory markers such as hs-CRP and MHR and CRR improved significantly as a result of decreased weight with orlistat treatment.

Keywords: Obesity, orlistat, monocyte-to-HDL ratio, monocyte-to-lymphocyte ratio, platelet-to-lymphocyte ratio, cardiac risk ratio, biomarkers

Introduction

The increase in the prevalence of obesity constitutes an important health problem worldwide [1]. According to World Health Organization data, it is known that in 2016, more than 1.9 billion adults worldwide are overweight and over 600 million individuals are obese [2]. In general, increased body mass index (BMI) is associated with an increased rate of death from cardiovascular disease [3]. It is known that excess body weight contributed to four million deaths worldwide in 2015, and over 320,000 deaths in the United States in 2014 [4]. Due to increasing living standards, physical activity and behavioral changes, which are the cornerstone of weight management, are generally limited and difficult to maintain. Pharmacotherapy for obesity can be considered if patients have a BMI of 30 kg/m^2 or greater or BMI of 27 kg/m^2 or greater with weight-related comorbidities [5].

New inflammatory markers have been identified in recent years and found an association with many cardiovascular diseases. Some of those; neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), monocyte-to-High Density Lipoprotein ratio (MHR), platelet-to-lymphocyte ratio (PLR), plasma atherogenic index (PAI), and cardiac risk ratio (CRR). Many of these markers can be obtained by simple biochemical measurements and are associated with especially increased cardiovascular disease [6-10]. These markers indirectly provide us with a lot of information. Although they have been tested in many different diseases and conditions, how they have been affected in patients receiving orlistat therapy due to obesity has never been evaluated before.

Many health problems such as type 2 diabetes mellitus, hypertension, dyslipidemia and coronary heart disease in obese patients are medical reasons for weight loss. The higher the BMI, the greater the risk of morbidity and mortality. It is obvious that the relationship between BMI and mortality is similar for all races and ethnicities. [11]. The goal of therapy is to prevent, treat, or reverse the complications of obesity and improve the quality of

***Coresponding Author:** Zafer Yalim, Afyonkarahisar Health Sciences University, Faculty of Medicine, Department of Cardiology, Afyonkarahisar, Turkey, E-mail: zaferyalm@yahoo.com.tr

life. Usually, lifestyle measures, pharmacologic therapy, and bariatric surgery are used in treatment [11,12]. Orlistat is an inhibitor of intestinal and pancreatic lipases that was first licensed for the treatment of overweight and obesity [14]. Orlistat has been shown to reduce weight in obese subjects and decrease the risk of cardiovascular disease. Although orlistat-induced weight reduction has recently been associated with a decrease in serum levels of both IL-6 and hs-CRP in obese subjects [15,16]. İt is not known how new inflammatory markers (such as NLR, MLR, MHR, PLR, PAI, CRR) are affected by orlistat treatment. The main purpose of this study is to determine the effect of orlistat, often used in the treatment of obesity, on the inflammation markers mentioned above.

Materials and Methods

Study population

In this retrospective study, 241 patients were enrolled who apply to the cardiology and internal medicine clinic in Afyonkarahisar Healthy Science University, between October 2018 - 2019. 197 patients (18 to 65 years old) who received orlistat treatment for the first time were included in the study. All of the participants in the study were selected from those received orlistat treatment at least three times a day. Patients with a body weight index (BMI)> 35 kg / m2 and with diet loss of at least 2.5 kg for four consecutive weeks were included in the study. Height (cm), weight (kg) were evaluated and BMI was calculated in all patients. All data before the treatment and at the 3rd-month control after orlistat treatment were recorded. 44 patients were excluded from the study due to exclusion criteria and lack of data. Patients with an active infection, chronic inflammatory diseases (such as Chrone's disease, rheumatoid arthritis, vasculitis), renal failure (Presence of Chronic renal failure (CRF) stage >3 and glomerular filtration rate of lower 59 mL/min/1.73m2), hepatic disorders, malignancy, using statin and anti-inflammatory drug, thyroid hormone disorders or acute coronary syndrome were excluded from the study. Our study was approved by the Institutional Local Ethics Committee (number of decision: 2019/220).

Laboratory analysis

All participants laboratory results collected from patient records. Samples of blood tests performed after 12 hours of fasting on admission to hospital. Blood samples were centrifuged at speed of 1600 bpm for 15 minutes. Roche Cobas C501 autoanalyser system (Roche, Rotkreuz, Switzerland) was used for all biochemical parameters [such as fasting blood glucose, serum creatinine, sodium, potassium, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein (HDL-C), triglyceride (TG)]. Blood samples were taken into standardized tubes containing dipotassium ethylenedinitrilo tetraacetic acid for complete blood count (CBC). And XN-2000 Hematology system (Bornbarch, Norderstedt, Germany) was used for CBC analysis. NLR, MLR, MHR, PLR were calculated by dividing. The PAI was calculated as the logarithm [log (TG/HDL-C)] of the ratio of plasma TG to HDL, measured in milligrams per deciliter. CRR was calculated as TC to HDL cholesterol ratio.

Statistical Analysis

For statistical analysis, we used the SPSS for windows version 23.0 (SPSS Inc., Chicago, IL, USA) software package. The categorical data was studied using frequency analysis. The Kolmogorov-Smirnov test was used for normality. Continuous variables with normal distribution were reported as the mean±standard deviation and categorical variables were expressed as the number of patients and percentages. The paired samples t-test was used to compare parametric variables and the Wilcoxon test was used to compare nonparametric variables, before and after treatment. In this study, $p<0.05$ was considered to indicate statistical significance.

Results

A total of 197 patients with treatment of orlistat (mean age 47.13±10.9 years) were enrolled. The gender ratios of the patients were male (%46.7) and female (%53.3). All demographic characteristics of the patients are presented in table 1.

Table 1. Demographic characteristics of study group

Demographic Variables	Patient number: 197
Age (mean ± standard error)	47.13±10.9
Gender (Male / Female), n (%)	92/105 (%46.7/%53.3)
DM, n (%)	73 (%37.1)
HT, n (%)	47 (%23.9)
HL, n (%)	30 (%15.2)
CAD, n (%)	2 (%1)
CRF, n (%) (Stage 1-2)	3 (%1.5)
Smoking, n (%)	32 (%16.24)

Abbreviations; DM: Diabetes mellitus, HTN: Hypertension, HL: Hyperlipidemia, CAD: Coronary artery disease, CRF: Chronic renal failure, n: number

In the comparison of patients before and after treatment, BMI was significantly decreased and the mean change was 3.4054 ($p<0.001$). The change of BMI and hs-CRP was shown in Figure-1. Compared to pre-treatment levels, neutrophil (5.71±1.9, 5.39±1.5, $p=0.016$), monocyte (0.572±0.207, 0.508±0.164, $p<0.001$), and platelets (309.09±102.1, 276.08±60.2, $p=0.023$) were significantly decreased after orlistat treatment. Also, significant improvement was observed in the lipid profile of the patients after orlistat treatment. When the inflammatory parameters were examined, a significant decrease in hs-CRP, in MHR, and in CRR after treatment were observed (for all, $p<0.05$). All data of the study group before and after orlistat treatment were presented in Table 2.

In addition, subgroup analyses of the patients were made according to gender. And significant changes in BMI, total cholesterol, triglyceride, LDL and HDL cholesterol, hs-CRP, and CRR were observed in both groups ($p<0.05$). Also, after orlistat treatment, a significant difference was observed between PLR in the female group and MHR, and monocyte in the male group. Besides, we found a difference in MLR and PAI that did not reach statistical significance in the male group. All subgroup analyzes performed by gender are presented in Table 3.

Table 2. Clinical variables before orlistat treatment and after 3 months

Variables	Before Orlistat	After Orlistat	Change	p value
BMI, kg/m²	45.96 ± 6.9	42.56 ± 6.1	-3.4054	<0.001*
Fasting Glucose, mg/dl	105.1 ± 34.9	100.4 ± 28.7	-4.7239	0.044*
Creatinine, mg/dl	0.71 ± 0.14	0.70 ± 0.14	-0.0074	0.325
ALT, mg/dl	20.6 ± 11.1	20.01 ± 11.7	-0.5878	0.367
AST, mg/dl	20.41 ± 16.9	19.88 ± 7.5	-1.5326	0.198
White blood cell, x10³/uL	8.56 ± 2.15	8.46 ± 2.19	-0.0928	0.483
Hemoglobine, g/dl	13.74 ± 1.4	13.61 ± 1.3	-0.1319	0.117
Neutrophil, x10³/uL	5.71 ± 1.9	5.39 ± 1.5	-0.3280	0.016*
Lymphocyte, x10³/uL	2.66 ± 1.9	2.43 ± 0.83	-0.2337	0.078
Monocyte, x10³/uL	0.572 ± 0.207	0.508 ± 0.164	-0.640	<0.001*
Mean platelet volüme,	9.26 ± 1.23	9.29 ± 1.09	+0.0309	0.593
Platelet, 10³/mm³	309.09 ± 102.1	276.08 ± 60.2	-33.005	0.023*
Total Cholestrol, mg/dl	185.1 ± 34.7	174.8 ± 34.1	-10.2928	<0.001*
Triglyceride, mg/dl	156.8 ± 59.8	143.3 ± 50.09	-13.5213	<0.001*
LDL-C, mg/dl	126.17 ± 33.9	118.88 ± 32.8	-7.2862	<0.001*
HDL-C, mg/dl	44.26 ± 9.66	45.62 ± 9.28	+1.3565	0.005*
hs-CRP, mg/dl	0.88 ± 0.52	0.67 ± 0.28	-0.2026	<0.001*
NLR	2.494 ± 1.34	2.466 ± 1.17	-0.0282	0.781
MHR	0.0135 ± 0.0057	0.0116 ± 0.0049	-0.00194	<0.001*
MLR	0.237 ± 0.104	0.223 ± 0.084	-0.0146	0.091
PLR	131.9 ± 84.4	125.9 ± 51.05	-6.024	0.323
PAI	0.528 ± 0.21	0.494 ± 0.28	-0.0347	0.068
CRR	4.32 ± 1.07	3.94 ± 0.92	-0.3870	<0.001*

Data are shown as mean±standard deviation (mean±SD) or percentage (%).The difference (Δ) are shown as change in values before and after treatment. Abbreviations: BMI: body mass index, LDL-C: Low-density lipoprotein cholestrol, HDL-C: High-density lipoprotein cholestrol, WBC: white blood cell, NLR: Neutrophil-to-lymphocyte ratio, MLR: monocyte-to-lymphocyte ratio, MHR: monocyte-to-High Density Lipoprotein ratio, PLR: platelet-to-lymphocyte ratio, PAI: plasma atherogenic index, CRR: Cardiac risk ratio. hs-CRP: high sensitive c reactive protein , * represents the significant p-values <0,05.

Table 3. Analysis of Male and Female groups

Variables	Male, n:92 Before-After Orlistat	p value	Female, n:105 Before-After Orlistat	p value
BMI, kg/m²	45.11±7.7 - 41.84±6.5	<0.001*	46.7±5.95 – 43.1±5.63	<0.001*
Platelet, 10³/mm³	316.7±64.2 – 269.7±52	<0.001*	302.4±75.4 - 282.2±65.6	<0.001*
T. Cholestrol, mg/dl	183.9±34.9 - 171.1±32.3	<0.001*	185.4±34.8 - 175.8±34.7	<0.001*
Triglyceride, mg/dl	171.01±80.3 - 155.6±63	0.122	152.9±52.6 – 139.9±45.6	<0.001*
LDL, mg/dl	125.9±31.7 - 117.7±30.7	0.007*	126.2±34.6 - 119.1±33.5	<0.001*
HDL, mg/dl	40.9±6.9 - 42.8±7.5	0.086	45.1±10.1 - 46.3±9.5	0.024*
hs-CRP, mg/dl	0.79±0.3 - 0.65±0.2	0.002*	0.90±0.56 - 0.68±0.3	<0.001*
NLR	2.45±1.29 - 2.60±1.37	0.270	2.53±1.38 - 2.34±0.96	0.184
MHR	0.0144±0.006 - 0.0113±0.004	<0.001*	0.0127±0.005 - 0.0118±0.005	0.172
MLR	0.241±0.11 - 0.219±0.07	0.082	0.234±0.09 - 0.226±0.09	0.515
PLR	128.7±106 – 125.6±53.1	0.798	134.7±58.9 - 122.1±49.4	0.049*
PAI	0.588±0.22 - 0.526±0.23	0.087	0.512±0.208 - 0.485±0.29	0.218
CRR	4.61±1.1 - 4.1±0.9	<0.001*	4.25±1.03 – 3.89±0.91	<0.001*

Data are shown as mean±standard deviation (mean±SD) or percentage (%).The difference (Δ) are shown as change in values before and after treatment. Abbreviations: BMI: body mass index, LDL-C: Low-density lipoprotein cholestrol, HDL-C: High-density lipoprotein cholestrol, NLR: Neutrophil-to-lymphocyte ratio, MLR: monocyte-to-lymphocyte ratio, MHR: monocyte-to-High Density Lipoprotein ratio, PLR: platelet-to-lymphocyte ratio, PAI: plasma atherogenic index, CRR: Cardiac risk ratio. * represents the significant p-values <0,05.

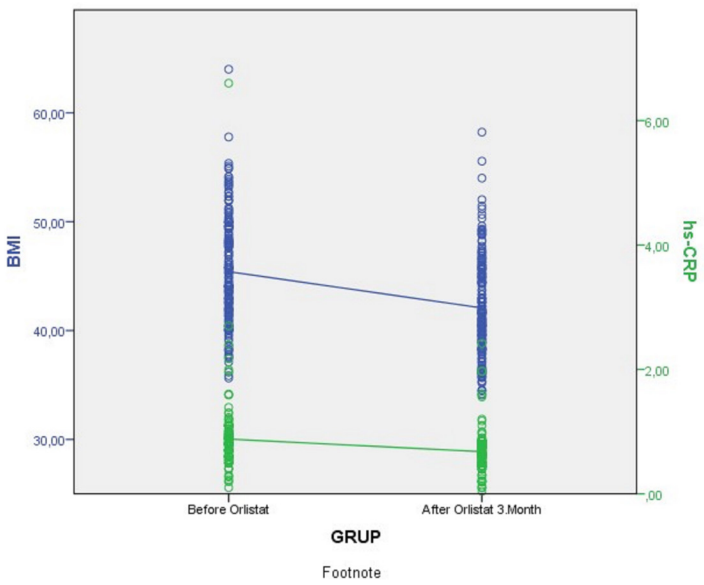

Figure 1. Change in BMI and hs-CRP before and after orlistat treatment

Discussion

Obesity is associated with systemic low-grade inflammation which is reaching alarming rates worldwide among both children and adults [17]. To the best of our knowledge, our study is the first to explore the effect of orlistat treatment on recent inflammatory markers. In this study, we showed the positive effect of orlistat treatment on inflammatory markers such as hs-CRP, MHR, CRR, and PLR. And we know that these markers can foresee future cardiovascular events and death. Even indirectly we think orlistat treatment may have a positive effect on future cardiovascular events.

Overweight and obesity is associated with a propensity towards the development of dyslipidemia, insulin resistance, hyperglycemia, hypertension, and a state of chronic low-grade inflammation, leading to an increased risk of cardiovascular morbidity and mortality [18,19]. In the study of Madsen et al., 10% weight loss in obese individuals has been shown to be associated with hs-CRP and plasma fibrinogen reduction [20]. In another study, a multidisciplinary program aimed to reduce body weight in obese women through lifestyle changes was associated with a reduction in markers of vascular inflammation (such as IL-6, IL-18, and hs-CRP) [21]. İn the same study, researchers suggested that the vascular inflammatory markers that improved after 2 years of follow-up are linked to future thrombotic events through mechanisms of plaque destabilization. In the one-year follow-up study of Samuelsson et al., IL-6 and TNF-alpha decreased significantly compared to the control group in the group receiving orlistat [22]. When the literature data are evaluated, the positive effects of orlistat treatment and weight loss on inflammatory markers are seen, but the cost of use of these markers is high and it is difficult to evaluate them practically. In our study, we found that inflammatory markers such as MHR, and CRR decreased with orlistat treatment. Evaluating these tests easily and cheaply can contribute to the follow-up and treatment of patients.

A growing body of evidence has suggested the role of low grade inflammation as a link between obesity, insulin resistance, and endothelial dysfunction. Increased serum levels of inflammatory biomarkers, such as hs-CRP have been reported in obese subjects and have been related to the degree of insulin resistance and endothelial dysfunction [23]. A number of epidemiological studies have demonstrated an association of hs-CRP levels with increased risk of peripheral vascular disease, stroke, sudden cardiovascular death, and myocardial infarction [24]. In a study conducted in our country, a significant decrease in IL-6 and hs-CRP was reported in 36 obese individuals with 6-month orlistat treatment [15]. In the prospective study of Hsieh et al.; significant improvements were observed in BMI, body fat, waist circumference, insulin resistance, hs-CRP, leptin, and adiponectin levels compared to the control group in the orlistat group in a one-year follow-up [16]. Considering our results, we found that hs-CRP values decreased significantly within 3 months with orlistat treatment. This effect was directly related to weight loss in patients. Indirectly, we can say that the decrease in hs-CRP level is associated with decreased cardiovascular events if weight loss is maintained.

It is known that orlistat treatment has positive effects on the lipid and glucose profiles in different patient groups [24-25]. When our study results were evaluated, similar to the literature data, an improvement in lipid and glucose profile was observed in the 3rd month of treatment. These effects of orlistat treatment are well known, but the effect on the recently identified inflammatory markers is still uncertain. In recent years, these markers have also been found in many different diseases and conditions from whole blood and routine biochemistry parameters. They have been proven to correlate well with established inflammatory markers such as hs-CRP and have a prognostic value among others in patients with coronary artery disease, heart failure, and malignancies [26]. In the study of Osadnik et al., it has been shown that MHR and NLR are associated with hs-CRP and fibrinogen among inflammatory markers in young healthy adults with obesity [27]. In the same study, a significant positive correlation was found between PLR and hs-CRP and fibrinogen in both overweight and obese groups. In our study, PLR showed a marked decrease with orlistat treatment, but probably famale sex had an effect. When we look at the MHR change, there was a significant decrease in both the whole group and the male group. Also, since the subgroup analysis of our study was evaluated, MHR and PLR showed different results by gender. These results made us think that the inflammatory response is different by gender.

Numerous studies have shown that inflammation is associated with an increased number of neutrophils and monocytes, while lymphocytopaenia is a common response to physiological stress [28,29]. Recently, a growing body of evidence emphasizes that the monocyte and macrophage differentiation and activation are key processes in the development of atherosclerosis [30]. When the results of our study were evaluated, there was a decrease in the number of neutrophils, monocytes, and platelet count with orlistat treatment, but no significant change was observed in NLR, MLR, and PLR. If our study was a follow-up study, perhaps we could show the cardiovascular clinical benefit of this reduction in neutrophils, monocytes, and platelet. NLR, MLR, and PLR could also have changed significantly. These results need to be tested in studies involving a larger number of patients because different results can be obtained in different groups.

CRR was found to be the best predictor of ischemic heart disease (IHD) risk in several observational prospective studies, because of the high prevalence of moderate hypertriglyceridemia among patients with IHD [31]. Variation in the CRR may be associated with more substantial alterations in metabolic indices predictive of IHD risk and related to the insulin resistance [32]. Considering the CRR results of our study, it was seen that it decreased significantly with orlistat treatment. We think it is important that this effect occurs even in 3 months of treatment. Whether this benefit is associated with orlistat therapy should be tested in a randomized controlled trial. Considering the results of our study, significant improvement is observed in new inflammatory markers such as CRR, and MHR by losing weight with orlistat treatment. If these patients are followed for a longer period, perhaps the frequency of cardiovascular events will be less visible.

Study Limitation

There are a few limitations of our study that should be considered. The major limitation of this study was the retrospective, single centre design and there was no control group. The small number of cases was another problem. These results, which were observed due to the absence of control group, could not be explained only with orlistat treatment, perhaps similar results could be followed in case of weight loss only by diet. Our results need to be supported with more comprehensive studies. In addition, side effects that may be due to orlistat could not be presented in the study due to a lack of data. Another limitation was that medical treatment of patients was not examined in detail, but we think this did not affect our outcome since we exclude statin used patients. Another limitation; the presence of patients with chronic diseases such as diabetes and hypertension in the study group may have influenced our results.

Conclusion

In our study, we observed that inflammatory markers such as hs-CRP and MHR and CRR improved significantly as a result of decreased weight with orlistat treatment. The easy and cheap evaluation of these tests can make a significant contribution to the follow-up and treatment of patients. Besides, these findings may implicitly indicate that these patients are less likely to develop cardiovascular events.

Conflict of interests

The authors declare that they have no conflict of interest and any financial disclosures.

Financial Disclosure
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Ethical approval
The study was approved by the local ethics committee.

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