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Original Article

Does tadalafil 5 mg/day affect lymphocyte to monocyte and monocyte to high-density lipoprotein ratios in patients with erectile dysfunction?

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Abstract

Aim: To investigate the effects of using 5 mg/day tadalafil on inflammatory indicators including lymphocyte to monocyte ratio (LMR) and monocyte to high-density lipoprotein ratio (MHR) in patients with erectile dysfunction (ED).

Material and Methods: This retrospective study included 62 subjects that 31 patients with ED and 31 healthy controls with a normal erectile function. The patients with ED were given a daily 5 mg dose of tadalafil over eight weeks. Baseline and post-treatment erectile function was evaluated using the International Index of Erectile Function (IIEF-5). Changes in IIEF-5 score and inflammatory indicators including LMR and MHR have compared both in ED patients and with controls.

Results: The patients and the controls were statistically comparable with respect to age, Diabetes Mellitus, hypertension, coronary artery disease, CRP, testosterone, serum creatinine, lipid profile, LMR, and MHR. The mean IIEF-5 score was 22.97 vs 14.32 (p=0.001) in control and patients with ED, respectively. Having been used 5 mg of tadalafil per day over 8 weeks, an increase in IIEF-5 score (p=0.001) and a decrease in the number of monocytes (p=0.008) were detected in patients with ED. However, there was no statistically significant difference found in LMR and MHR before and after the treatment.

Conclusion: According to the results of this study, no significant effect was found daily use of 5mg tadalafil on inflammatory indicators including LMR and MHR. The decrease in the number of monocytes that play a key role in inflammation may have been considered a response to treatment, however, randomized prospective studies are needed to evaluate the relationship among LMR, MHR and tadalafil treatment.

Keywords: Erectile dysfunction; inflammation; lymphocyte to monocyte ratio; monocyte to HDL ratio; tadalafil

INTRODUCTION

Erectile dysfunction (ED) that is considered a clinical symptom caused by the underlying diseases is defined as the inability to achieve or maintain the penile erection requiring for satisfactory sexual performance (1).

Due to the unique vascular structure of the penis, the most common cause of ED is penile arterial disease, accounting for about 80% of cases (2). Endothelial dysfunction and inflammation have been shown as common etiological factors of cardiovascular disease (CVD) and ED in the previous studies in the literature (3,4). Monocyte oxidative activation has also been specified to have increased in the very early period of inflammation that causes endothelial dysfunction (5). In contrast to monocytes, many studies have shown that high-density lipoprotein (HDL) which has antioxidative and anti-inflammatory properties on the vascular endothelium, has a strong however inverse relationship with the occurrence of cardiovascular events. HDL also has endothelial protective effects, such as preventing low-density lipoprotein (LDL) oxidation and monocyte activation, transmigration, and differentiation (6,7).

In recent years, inflammatory markers such as lymphocyte to monocyte ratio (LMR) and monocyte to HDL ratio (MHR) have been used to evaluate the systemic inflammatory response associated with a variety of benign and malignant diseases (8). Moreover, low LMR has been shown as a marker that closely correlated with CVD (9,10).

Another novel marker defined to evaluate inflammation is MHR. In the very first studies it had been reported that the increase in MHR to be associated with adverse outcomes of cardiovascular diseases. Then, MHR has been reported to be associated with inflammation as well as coronary slow flow (11).

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The aim of this study was to investigate the effect of once-a-day (OAD) 5 mg dose of tadalafil for eight weeks on MHR and LMR levels in patients with ED. As far as it is known, there is no study available that has evaluated the effect of tadalafil on LMR as well as MHR levels in patients with ED to date.

MATERIAL and METHODS

This study conducted in compliance with the ethical principles of the Helsinki Declaration. Ethical approval was granted by the Ondokuz Mayıs University Clinical Research Ethics Committee (OMU KAEK 2019/158). Informed consent was obtained from all patients prior to their database inclusion. This study was also registered at ClinicalTrials.gov (NCT03918993)

The present study was designed as a single-center, retrospective, chart review of heterosexual male patients who refer to our urology outpatient clinic for ED and other urological disorders during the period of July 2017 - October 2018. All participants enrolled in the study were selected by random sampling method. A total of 31 male patients between the ages of 39-65 with organic ED for more than one year included in the study as an ED group. Thirty-one age-matched men who were sexually active with regular monogamous heterosexual relationships during the last one year was taken as a control group. When HDL values are taken into account, it is sufficient to include a total of 62 subject with 95 % confidence and 98,6 % test power (11).

The patients with systemic autoimmune and inflammatory disease, congestive heart failure, chronic renal failure, and chronic hepatobiliary disease, chronic lung disease, and thyroid dysfunction, patients with acute infection, patients with neurological deficits, metabolic syndrome and malignancy were excluded from the study. In addition, urogenital examination of the external genital organs in patients with pathology was excluded. Patients with a history of prostate, penile or pelvic surgery or radiotherapy, as well as patients receiving anticoagulant, beta-blocker, antidepressants and antipsychotics, hormonal therapy, patients with alcohol and smoking were also excluded from the study.

Evaluation of subjects

A detailed medical and sexual history of all the patients and the subjects were obtained. Additional systemic diseases and drugs they used and their previous surgeries were questioned. Then, the patients underwent urological, neurological and systemic examination. A detailed psychiatric examination was performed to confirm in the patients with organic erectile dysfunction to eliminate psychological erectile dysfunction. During the psychiatric examination, those were evaluated in terms of whether there was an erection in the morning, masturbation frequency and erection during masturbation. Furthermore, intra-cavernous injection of 40 mg papaverine was also used to exclude patients with psychogenic ED.

Sexual function of each participant was evaluated using Turkish-validated five-item version of the International Index of Erectile Function (IIEF-5)(12). Each question was scored from 1 (almost never or never) to 5 (almost always or always). Patients were sort out as having severe dysfunction (score= 5-7), moderate dysfunction (score = 8-11), mild-to-moderate dysfunction (score = 12-16), mild dysfunction (score = 17-21), and no ED (score = 22-25). While the ED group received OAD 5 mg dose of tadalafil for eight weeks, the control group did not take any medication.

Laboratory analysis

Morning samples of laboratory tests of the participants were obtained in fasting condition. Complete blood count including monocyte and lymphocyte was evaluated with XN- 550 analyzer (Sysmex Corporation, Kobe, Japan). Lipid metabolism was evaluated using a biochemistry analyzer (cobas c 311, Roche) for the determination of total cholesterol (TC), triglycerides (TG), HDL and LDL. Total testosterone (TT) was performed using an analyzer (Cobas e 411 Roche). Monocyte and lymphocyte values were calculated in µ/L, blood cholesterol values in mg / dl and TT in ng / mL. In the calculation of MHR and LMR, the study conducted by Vahit D et al. taken as reference was used. The units of numerical variables are arranged according to the values in this study (13).

Statistical analysis

The data were analyzed using Statistics Package for Social Sciences version 24 (IBM SPSS®, Armonk, NY). Independent samples t-test was used to compare normally distributed data according to the control and treatment groups. The dependent samples t-test was used to compare the pre- and post-treatment values of the treatment group. The chi-square test was used to examine categorical data. The analysis results were presented as the mean ± standard deviation for quantitative data and as frequency (percentage) for qualitative data. The significance level was taken as $p < 0.05$.

RESULTS

There was no statistically significant difference in terms of the mean age between the ED and control groups (47.68 ± 8.53 vs 51.42 ± 7.72 years, p=0.07). The mean body mass index (BMI) was 26.70 ± 3.8 in the ED group and it was 26.46 ± 2.2 in the control group, (p=0.767). Comorbidities including Hypertension (p=0.108), Diabetes Mellitus (p=0.061), and CAD (p=0.151) as well as serum lipid profiles such as TC (p=0.076), LDL (p=0.389), HDL (p=0.969), TG (p=0.814), were similar in the ED and control groups. Fasting glucose (p=0.443), serum creatinine (SCr) (p=0.813), C-reactive protein (CRP) (p=0.161) and TT (p=0.208) values were found to be statistically similar in both groups.

Although the mean number of monocytes count was similar in the ED and the control group (635.97 ± 133.37 and 637.42 ± 161.33 µl, p=0.969), the mean lymphocyte count was statistically significant (2670.32 ± 565.16 and 2380 ± 539.8 µl, p=0.043) when both groups were compared. As expected, the mean IIEF-5 score was 14.32

± 2.99 in the ED group and 22.97 ± 1.3 in the control group, and there was a statistically significant difference (p = 0.001). No statistically difference was detected when compared to LMR and MHR between the ED and control group. LMR was 4.33 ± 1.09 vs 3.87 ± 1.1 (p=0.102) and MHR was 16.46 ± 5.21 vs 16.07 ± 5.14 (p= 0.767) in the ED group and control group, respectively. Pre-treatment demographic and laboratory parameters were shown in Table 1.

Table 1. Demographic characteristics and laboratory findings

	Controls (n=31)	Patients (n=31)	p Value
Age (year)	47.68 ± 8.53	51.42 ± 7.72	0.075
BMI (kg/m²)	26.46 ± 2.2	26.70 ± 3.8	0.767
Hypertension, n (%)			0.108
Negative	28 (90.3)	22 (71)	
Positive	3 (9.7)	9 (29)	
Diabetes mellitus, n (%)			0.061
Negative	28 (90.3)	21 (67.7)	
Positive	3 (9.7)	10 (32.3)	
CAD, n (%)			0.151
Negative	31 (100)	29 (93.5)	
Positive	--	2 (6.5)	
Glucose, mg/dL	112.68 ± 42.39	120.94 ± 41.74	0.443
Serum creatinine, mg/dl	0.88 ± 0.13	0.87 ± 0.13	0.813
C-reactive protein, mg/dl	0.19 ± 0.04	0.2 ± 0.03	0.161
Testosterone, ng/mL	3.48 ± 1	3,89 ± 1.48	0.208
Total cholesterol, mg/dl	211.48 ± 40.09	194.61 ± 33.28	0.076
Triglyceride, mg/dL	192.94 ± 77.32	188.68 ± 64.24	0.814
LDL, mg/dL	136.16 ± 36.65	128.06 ± 36.79	0.389
HDL, mg/dL	42.23 ± 11.63	42.06 ± 20.07	0.969
IIEF-5 score	22.97 ± 1.3	14.32 ± 2.99	0.001
Lymphocyte count, µ/L	2670.32 ± 565.16	2380 ± 539.8	0.043
Monocyte count, µ/L	637.42 ± 161.33	635.97 ± 133.37	0.969
LMR	4.4 ± 1.7	3.9 ± 1.3	0.161
MHR	16.07 ± 5.14	16.46 ± 5.21	0.767

CAD: Coronary Artery Disease, IIEF-5: International Index of Erectile Function-5, LDL: Low-Density Lipoprotein, HDL: High-Density Lipoprotein, LMR: Lymphocyte to Monocyte Ratio, MHR: Monocyte to HDL Ratio

Table 2. Pre- and post-treatment values of patients with ED

	Pre-tadalafil (n=31)	Post-tadalafil (n=31)	p Value
IIEF-5 score	14.32 ± 2.99	22.26 ± 1,73	**0.001**
Lymphocyte count, µ/L	2380 ± 539.8	2405.61 ± 543.76	0.853
Monocyte count, µ/L	635.97 ± 133.37	563.71 ± 92,94	**0.008**
HDL, mg/dL	42.06 ± 20.07	38.15 ± 6.6	0.282
MHR	16.46 ± 5.21	15.33 ± 4.1	0.269
LMR	3.9 ± 1.3	4.3 ± 0.96	0.201

IIEF-5: International Index of Erectile Function-5, HDL: High-Density Lipoprotein, LMR: Lymphocyte to Monocyte Ratio, MHR: Monocyte to HDL Ratio

In the ED group, as compared to the before and after treatment parameters following the use of OAD 5 mg dose of tadalafil for 2 months, a statistically significant increase in the mean IIEF-5 score (14.32 ± 2.99 vs 22.26 ± 1.73, p=0.001) and a significant decrease in the mean monocyte count (635.97 ± 133.37 vs 563.71 ± 92.94, p=0.008) were detected. Although the mean lymphocyte count (2670.32 ± 565.16 vs 2405.61 ± 543.76) decreased, this decrease was not statistically significant (p=0.079). However, there was no statistically significant difference between MHR (16.46 ± 5.21 vs 15.33 ± 4.1, p=0.269) and LMR (4.33 ± 1.09 vs 4.32 ± 0.97, p=0.958) over time. The outcomes of pre- and post-treatment of the ED group were shown in Table 2.

Table 3. Comparison of the control group and post-treatment ED patients			
	Controls (n=31)	Post-treatment ED (n=31)	p Value
IIEF-5 score	22.97 ± 1.3	22.26 ± 1.7	0.659
Monocyte count, µ/L	637.42 ± 161.33	563.71 ± 92.94	**0.031**
MHR	16.07 ± 5.14	15.32 ± 4.1	0.094
Lymphocyte count, µ/L	2670.32 ± 565.16	2405.61 ± 543.76	0.065
LMR	4.44 ± 1.4	4.32 ± 0.96	0.077

IIEF-5: International Index of Erectile Function-5, LMR: Lymphocyte to Monocyte Ratio, MHR: Monocyte to HDL Ratio

The comparison of the ED group and the control group after treatment was shown in Table 3. Compared the ED group and the control group after the treatment, there was no statistically significant difference was found in MHR (16.07 ± 5.14 vs 15.32 ± 4.1, p= 0.094), LMR (4.44 ± 1.4 vs 4.32 ± 0.96, p= 0.077), and the mean IIEF-5 scores (22.97 ± 1.3 vs 22.26 ± 1.7, p= 0.659).

DISCUSSION

In this study, it was found that in patients who received daily 5 mg tadalafil for 8 weeks for the management of ED, there were no statistically significant alterations in MHR and LMR values. However, the reduction in the mean monocyte count was determined statistically significant. Additionally, there was not statistically significant difference neither before nor after the treatment in the MHR and LMR values of the patients as compared to the controls. The decrease in the number of monocytes counts that play a key role in inflammation may be considered a response to treatment in patients with ED receiving tadalafil 5 mg/day.

Atherosclerosis and endothelial dysfunction have a considerable role in the etiopathogenesis of both ED and CVD. The first stage, endothelial dysfunction causes a decrease in endothelium-dependent vasodilatation; later arterial insufficiency due to the degree of obstruction in the lumen of the artery is the basic changes detected in ED and CVD (14). Endothelial integrity deteriorates as a result of the destructive effect of the risk factors on the endothelium. Endothelial dysfunction causes a decrease in NO synthesis as well as a deterioration in the balance between NO and superoxide anions. It also loses its protective effect against atherosclerosis. Endothelial dysfunction causes mononuclear cells to attach to the endothelium, such as lymphocytes and monocytes, and then migrate to the sub-endothelial field. The oxidation of LDL induces the initiation of a series of inflammatory processes in the vessel wall and consequently atherosclerosis develops (15, 16).

In this study, the mean lymphocyte count in patients with ED was lower than the control group before 5 mg tadalafil treatment per day. This difference was statistically significant. However, there was no statistically significant difference between the controls and patients with ED in terms of LMR before the treatment as well. There was no significant difference in the mean lymphocyte count between the patients with ED and the controls, after the treatment. The lymphocyte counts were found to be inversely related to inflammation. However, these finding can be affected by many parameters.

Although inflammation begins as a local response after endothelial injury, it continues as a systemic process due to the increase of inflammatory mediators. It has been stated that higher monocyte count and lower HDL level are likely to be related to inflammation (17-19). The MHR is a novel inflammatory marker, defined as an independent predictor of CVD in patients with chronic kidney disease (20). Although there are many studies showing that MHR is a reliable marker for inflammation and oxidative stress and associated with progression of various cardiovascular diseases, the role of MHR as a risk as well as a prognostic factor in normal healthy individuals without CVD is not transparent (20-22).

There are a limited number of publications in the literature evaluating the relationship between ED and MRH. In a retrospective study, Kadihasanoglu et al. have compared 60 patients with ED and 60 non-ED men in terms of IIEF and MHR. Patients and control group were found to be similar in terms of risk factors. The mean monocyte count and MHR were found to be significantly higher in patients with ED than those non-ED men. MHR was also found negatively correlated with IIEF5 (23). Another prospective study with similar characteristic conducted by Cimen et al. have also stated that monocyte count and MHR were found to be higher in patients with ED than those non-ED men (24). Both studies reported that MHR is a marker that can be used in identification and follow-up in patients with ED. Contrary to the two studies mentioned above, in this study, no statistically significant difference was found between the ED patients and the healthy control group in terms of MHR both before and after the treatment. However, a statistically significant decrease was determined in the mean monocyte count in patients with erectile dysfunction after daily 5 mg tadalafil treatment for two months. In addition, a significant difference was also determined in the mean lymphocyte count in patients with ED than controls before treatment.

It is known in detail that tadalafil has a wide variety of protective effects on endothelium including to increase NO synthesize, to reduce inflammatory cytokines, to

repair endothelial injury with bone marrow-derived EPCs (25, 26). In addition, OAD 5mg of tadalafil for eight weeks has also been reported in a recent publication that it was an effective treatment approach in terms of achieving improvement in patients with ED (27). The secondary objective of our study was to evaluate changes in IIEF 5 score in patients receiving tadalafil treatment. It was also determined in this study that our findings are similar to the literature that OAD 5mg dose of tadalafil treatment at the end of 8 weeks showed a significant improvement in the IIEF 5 score of the patients.

This is a retrospective study with the number of subjects was relatively small in size. However, the use of power analysis to calculate the number of subjects to be included in the study has increased the confidence and power of the study. In the control group, it would be more meaningful to re-evaluate the numerical parameters, which are likely to change over time, such as monocyte and lymphocyte count, serum lipid profile, and IIEF5 score in ED patients. However, in this retrospective study, the control group was evaluated only once.

CONCLUSION

The use of LMR and MHR in the evaluation and follow-up of the treatment response of patients with ED was not found to be appropriate. We believe that it is difficult to provide standardization in clinical use because there are many diseases and risk factors affecting inflammatory markers. Moreover, the change in the calculation of MHR and LMR methods according to the publications is the most important reason for this idea.

Competing interests: The authors declare that they have no competing interest.

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Ethical approval: This study conducted in compliance with the ethical principles of the Helsinki Declaration. Ethical approval was granted by the Ondokuz Mayis University Clinical Research Ethics Committee (OMU KAEK 2019/158). Informed consent was obtained from all patients prior to their database inclusion. This study was also registered at ClinicalTrials.gov (NCT03918993).

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