

# Carotid artery intima media thickness can predict the response to phosphodiesterase 5 inhibitors in patients with moderate erectile dysfunction

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## Abstract

**Background:** Increased carotid artery intima-media thickness (CIMT) has been shown to be associated with erectile dysfunction (ED), but studies evaluating the efficacy of CIMT in predicting drug response are lacking in the literature.

**Aim:** We aimed to evaluate the efficacy of CIMT in predicting the response to phosphodiesterase-5 inhibitors (PDE5-I).

**Methods:** A total of 274 subjects were divided into two groups: ED patients ( $n = 150$ ) and controls ( $n = 124$ ). The patients in the ED group were further divided into the subgroups of severe, moderate, mild-moderate, and mild ED. Blood tests, carotid ultrasonography, and the International Index of Erectile Function-5 (IIEF-5) diagnostic tool were applied to all subjects. Tadalafil was administered to each patient. The patients were re-evaluated using the IIEF-5 questionnaire after 2 months of treatment. According to their response to medication, the patients were evaluated as responders or nonresponders.

**Outcomes:** Increased CIMT was significantly associated with the failure of PDE5-I therapy, especially in patients with moderate/mild-moderate ED.

**Results:** Fasting blood glucose, body mass index, and CIMT were significantly higher in the ED group compared to the control group ( $P = .021$ ,  $P = .006$ , and  $P < .001$ , respectively). The IIEF-5 score was significantly lower in the ED group ( $P < .001$ ). CIMT was significantly correlated with the IIEF-5 score. When the total patient group was evaluated, the CIMT value of the responders was significantly lower than that of the nonresponders ( $P = .001$ ). CIMT was significantly higher among the nonresponders with moderate/mild-moderate ED compared to the responders ( $P = .004$  and  $.008$ , respectively), while there was no significant difference in CIMT between the responders and nonresponders with severe or mild ED. A receiver operating characteristic (ROC) analysis of CIMT was performed for discrimination between nonresponders and responders with moderate/mild-moderate ED. The area under the ROC curve was 0.801 (0.682–0.921) ( $P = .001$ ), and the cutoff value was determined to be 0.825 mm, at which CIMT predicted the response to treatment with 65% sensitivity and 89% specificity.

**Clinical Implications:** Using a validated CIMT cutoff value can help the physician inform the patient about the possibility of drug failure and avoid attempting second-line therapy too soon.

**Strengths and Limitations:** There are three main limitations to our study. First, the number of participants was low. Second, ultrasound is a relatively subjective method, and third, all measurements were made by the same radiologist.

**Conclusion:** CIMT can be used as a predictor of response to PDE5-I therapies in patients with moderate/mild-moderate ED.

**Keywords:** erectile dysfunction; carotid intima media thickness; medical treatment; phosphodiesterase type 5 inhibitors.

## Introduction

Erectile dysfunction (ED) is defined as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance. Although ED is a benign disorder, it can affect physical and psychosocial health and may have a significant impact on the quality of life (QoL) of sufferers and their partners.<sup>1</sup> The pathophysiology of ED is usually multifactorial, with the most common etiology being vasculogenic disorders.<sup>2</sup> Significant evidence demonstrating the close relationship between ED and cardiovascular disease exists in the literature.<sup>3–5</sup> A higher prevalence of ED has been shown among patients with cardiovascular risk factors, such

as aging, smoking, diabetes mellitus, obesity, hypertension, and hyperlipidemia.<sup>6</sup> Early diagnosis plays a crucial role in preventing morbidity and mortality. Carotid artery intima media thickness (CIMT), which has been widely used since the 1980s, is a useful predictor of cardiovascular disorders.<sup>7–9</sup> Having similar risk factors and underlying pathological mechanisms, CIMT may also serve as a predictor of ED. Many studies have reported that an increase in CIMT is directly proportional to the severity of ED.<sup>10,11</sup>

Today, four potent phosphodiesterase-5 inhibitors (PDE5-Is) (tadalafil, sildenafil, vardenafil, and avanafil) are used for

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the first-line treatment of ED.<sup>12</sup> In the dose response studies of these drugs, approximately 80% of participants have reported improved erections; however, the response rate of patients with comorbidities such as diabetes mellitus is lower.<sup>13,14</sup> Porst et al. noted that up to 40% of men with ED might not respond sufficiently to the maximum dose of PDE5-Is.<sup>15</sup>

Studies that evaluate the efficacy of parameters in predicting response to PDE5-Is are lacking. To our knowledge, there is only one study in the literature that investigated the predictive value of CIMT for this purpose. However, in that study, the patients were not grouped according to the severity of ED.<sup>16</sup> In the current study, we aimed to evaluate the predictive value of CIMT in subgroups of patients formed according to the severity of ED.

## Methods

A total of 150 men aged between 40 and 70 years who presented to the urology outpatient clinic of Bursa Yuksek Ihtisas Training and Research Hospital between December 2018 and November 2019 with the complaint of ED were included in the study. As a control group, a total of 124 male volunteers who did not have ED were included.

Patient exclusion criteria were the following: age under 40 or over 70 years, inability to obtain consent, presence of endocrine diseases except type II diabetes mellitus, concomitant malignancies, psychiatric problems, previous penile or pelvic surgery/trauma, and penile curvature/Peyronie's disease.

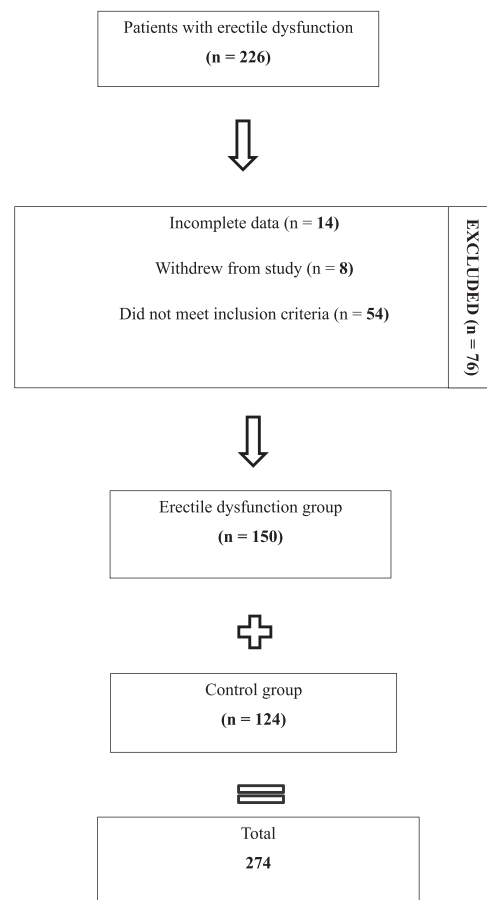
Additional exclusion criteria were ongoing treatment for ED, chronic liver failure, chronic kidney failure, neurological diseases, a low testosterone level ( $\leq 300$  ng/dL), or normal Doppler imaging findings.

The patients who did not meet any of the abovementioned exclusion criteria were included in the study. The flow chart of the study is presented in Figure 1. This prospectively designed study complied with the rules of the Declaration of Helsinki and was approved by the local ethics committee of Bursa Yuksek Ihtisas Training and Research Hospital (2011-KAEK-25) (approval number: 2014/23-01). Written informed consent was obtained from all participants before enrollment.

Complete blood count, fasting blood glucose, aspartate transaminase, alanine transaminase, hemoglobin A1c, blood urea nitrogen, creatinine, triglyceride, high-density lipoprotein, low-density lipoprotein, very low-density lipoprotein, total cholesterol, total testosterone, follicle-stimulating hormone, luteinizing hormone, and prolactin analyses were performed for each patient.

The International Index of Erectile Function-5 (IIEF-5) was used to assess ED.<sup>17</sup> Patients who 5-7, 8-11, 12-16, and 17-21 were classified as having severe ED, moderate ED, mild-moderate ED, and mild ED, respectively, while those scoring 22-25 were considered healthy and included in the control group. Initially, 10 mg of tadalafil on demand was administered to each patient with ED. Patients who did not benefit from the 10-mg dose were administered 20 mg. Patients who did not respond to 20 mg of tadalafil were evaluated as nonresponders. The patients were re-evaluated using the IIEF-5 questionnaire after 2 months of treatment.

Carotid ultrasonography was conducted using a high-resolution B-mode system (Aloka ProSound a7, Japan) with a 5-13-MHz linear transducer. The participants were scanned in a supine position with their neck extended and their chin



**Figure 1.** Flow-chart of the study.

in a normal position or turned contralateral to the examined side. CIMT was measured in the posterior wall of the bilateral common carotid arteries 1-2 cm proximally to the bifurcation, and the average values of the right and left CIMT were calculated for each patient.

Penile color Doppler ultrasonography was conducted using a high-resolution B-mode system (Aloka ProSound a7, Japan) with a 5-13-MHz linear transducer. Papaverine (50 mg) was injected intracavernously to evaluate arterial and venous flow. Arterial and venous blood flow was monitored at 5-minute intervals for 20 minutes for both cavernosal arteries. Psychogenic ED was detected on Doppler imaging based on a normal peak systolic velocity higher than 35 cm/s, end diastolic  $< 5$  cm/s, resistance index  $> 0.9$ , and a rigid erection obtained at the end of the test. A mean arterial flow of 5 cm/s in the right and left cavernosal arterial measurements was accepted as pathological.<sup>18</sup> All the measurements were performed by the same radiologist, who had Doppler ultrasonography experience of more than 10 years at the time of the study. Carotid ultrasonography was performed in all the participants (the patient group [responders and non responders] and the healthy group). Penile color Doppler ultrasonography was not performed in the healthy group.

## Statistical analysis

The IBM SPSS Statistics version 25 Windows software package was used for statistical analyses. The compliance of the data with the normal distribution curve was evaluated with the Shapiro-Wilk test. Continuous variables and categorical

**Table 1.** Comparison of the study groups according to demographic, laboratory, and sonographic parameters.

	Control group (n = 124)	ED group (n = 150)	P
Age, year	48 (43-65)	49 (40-69)	.847
Weight, kg	84 (68-94)	86 (45-128)	.120
BMI, kg/m <sup>2</sup>	27.9 (22.30-34)	29.4 (18-44.3)	.021
Smoking, No. (%)	72 (58.1)	45 (44.6)	.220
HT, No. (%)	32 (25.8)	28 (27.7)	.834
DM, No. (%)	12 (9.7)	25 (24.8)	.073
COPD, No. (%)	0 (0)	4 (4)	.572
CVD, No. (%)	8 (6.5)	12 (11.9)	.518
FBG, mg/dl	94 (73-117)	105 (54-387)	.006
HgA1c, No. (%)	5.5 (4.70-6.60)	5.60 (4.6-11.8)	.319
BUN, mg/dl	13 (8-21)	14 (6-30)	.344
Creatinine, mg/dl	0.82 (0.74-1.04)	0.84 (0.65-2.10)	.230
Total testosterone, ng/dl	369.97 (300-611.4)	368.65 (300-1083)	.614
Total cholesterol, mg/dl	217.16 (138.79-300.32)	205.48 (121.73-361)	.427
Hemoglobin, g/dL	15.30 (10.60-17.10)	15.20 (10.10-18.20)	.998
Mean CIMT, mm	0.63 (0.54-0.91)	0.80 (0.55-1.30)	<.001
IIEF-5 score	23.0 (22-25)	11.0 (5-20)	<.001

Abbreviations: BMI, body mass index; BUN, blood urea nitrogen; CIMT, carotid intima media thickness; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DM, diabetes mellitus; ED, erectile dysfunction; FBG, fasting blood glucose; HgA1c, hemoglobin A1c; HT, hypertension; IIEF-5, International Index of Erectile Function-5.

data were compared using the Student *t*-test, the Mann-Whitney U test, and the chi-square test. The *t*-test was used to compare pretreatment and posttreatment IIEF scores. The relationships between variables were examined with Pearson's correlation and Spearman's correlation tests. The receiver operating characteristic (ROC) curve was used to evaluate and compare the ability of CIMT to predict the response to medical treatment in patients with ED.  $P < .05$  was accepted as statistically significant.

## Results

A total of 274 men (150 patients with ED and 124 healthy men) were included in the study. The demographic data, laboratory results, and CIMT values of the ED and control groups are shown in Table 1. Fasting blood glucose, body mass index, and CIMT were significantly higher in the ED group than the control group ( $P = .021$ ,  $P = .006$ , and  $P < .001$ , respectively). The IIEF score was significantly lower in the ED group than the control group ( $P < .001$ ).

The correlation analysis of some parameters and IIEF-5 score is shown in Table 2. CIMT was significantly correlated with IIEF-5 ( $r = -0.494$ ,  $P < .001$ ).

The subgroup comparisons of the patients with ED are shown in Table 3. According to the results, the only significant difference between the ED subgroups was observed in CIMT ( $P = .012$ ).

Table 4 shows the comparison of the patients with ED according to whether they responded to drug therapy. The CIMT value of the responders was significantly lower than the value of the nonresponders ( $P = .001$ ). When the responders and nonresponders were compared according to the severity of ED, CIMT was significantly higher in the nonresponders with moderate/mild-moderate ED ( $P = .004$  and  $.008$ , respectively).

Figure 2 presents the ROC curve of CIMT for discrimination between nonresponders and responders among all patients with ED. The area under the ROC curve (AUC) was 0.706 (95% confidence interval: 0.604-0.809) ( $P = 0.001$ ). The cutoff value was determined to be 0.812 mm in all patients

**Table 2.** Correlation analysis between the IIEF-5 score and other variables.

	r	P
Age, year	-0.138	.116
Mean CIMT, mm	-0.494	<.001
BMI, kg/m <sup>2</sup>	-0.151	.083
FBG, mg/dl	-0.321	<.001
ALT, U/L	0.076	.388
AST, U/L	0.049	.576
HgA1c, %	-0.235	.007
BUN, mg/dl	-0.098	.263
Creatinine, mg/dl	-0.174	.046
Total cholesterol, mg/dl	0.052	.554
Total testosterone, ng/dl	-0.005	.957
Hemoglobin, g/dL	0.071	.415

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; BUN, blood urea nitrogen; CIMT, carotid intima media thickness; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DM, diabetes mellitus; ED, erectile dysfunction; FBG, fasting blood glucose; HgA1c, hemoglobin A1c; HT, hypertension; IIEF-5, International Index of Erectile Function-5.

with ED. CIMT predicted the response to treatment with 64% sensitivity and 77% specificity.

Figure 3 shows the ROC curve of CIMT for discrimination between nonresponders and responders among patients with moderate/mild-moderate ED. The AUC was 0.801 (95% confidence interval: 0.682-0.921) ( $P = 0.001$ ), and the cutoff value was determined to be 0.825 mm for these groups. CIMT predicted the response to treatment with 65% sensitivity and 89% specificity.

## Discussion

Erectile dysfunction (ED) is a common disease that affects 14%-70% of men aged 60 years or older.<sup>19</sup> Although the prevalence of ED increases with age, a significant proportion (5%) of men aged 40 years and younger suffer from this condition.<sup>20,21</sup> Since the introduction of the first PDE5-I in 1998, the treatment of ED has changed dramatically. PDE5-I drugs block the conversion of cyclic guanosine monophosphate into guanosine triphosphate, decrease intracellular calcium, cause

**Table 3.** Comparison of the ED subgroups according to demographic, laboratory, and sonographic parameters.

	Severe ED group (n = 42)	Moderate ED group (n = 45)	Mild-moderate ED group (n = 39)	Mild ED group (n = 24)	P
Age, years	50.0 (40-69)	50 (40-68)	50.5 (40-62)	47.5 (40-62)	.239
Weight, kg	85.5 (56-128)	85.0 (73.5-100)	87.5 (73-112)	82.1 (45-128)	.653
BMI, kg/m <sup>2</sup>	28.9 (20.8-41.2)	29.4 (24.6-35.8)	29.95 (24.1-35.5)	29.45 (18-44.3)	.948
HT, present/absent, No. (%)	13 (30.95)/29 (69.05)	6 (13.3)/39 (86.7)	12 (30.8)/27 (69.2)	10 (41.6)/14 (58.4)	.120
DM, present/absent, No. (%)	12 (28.6)/30 (71.4)	6 (13.3)/39 (86.7)	15 (38.5)/24 (61.5)	5 (20.8)/19 (79.2)	.139
COPD, present/absent, No. (%)	3 (7.1)/39 (92.9)	0 (0)/45 (100)	3 (7.7)/36 (92.3)	0 (0)/24 (100)	.304
CVD, present/absent, No. (%)	9 (21.4)/33 (78.6)	2 (4.4)/43 (95.6)	5 (12.8)/34 (87.2)	3 (12.5)/21 (87.5)	.198
FBG, mg/dl	108.5 (54-387)	104.0 (82-315)	104.5 (55-226)	98 (77-159)	.229
HgA1c, %	5.75 (5.00-11.8)	5.60 (4.60-11.3)	5.5 (4.7-8.4)	5.45 (4.60-9.1)	.102
BUN, mg/dl	14.0 (7.0-30)	14.0 (10-29)	14 (10-22)	12.5 (6-20)	.789
Creatinine, mg/dl	0.89 (0.67-1.6)	0.84 (0.74-2.1)	0.83 (0.73-1.39)	0.84 (0.65-1.02)	.168
Total testosterone, ng/dl	379.06 (300-1083)	358.37 (300-779)	341.44 (300-618.78)	391.5 (300-1058)	.430
Total cholesterol, mg/dl	199.91 (121.73-361)	214.0 (134.62-278.76)	204.84 (144-286.93)	205.62 (146.05-330)	.947
Hemoglobin, g/dL	15.1 (10.1-17.9)	14.9 (13.2-18.2)	15.5 (13.5-17.9)	15.25 (11.1-17.8)	.572
Mean CIMT, mm	0.84 (0.63-1.28)	0.85 (0.57-1.09)	0.76 (0.56-1.30)	0.72 (0.55-0.90)	.012
IIEF-5 score	6 ± 0.81	9.5 ± 1.1	14 ± 1.3	18.3 ± 1.1	<.001

Abbreviations: BMI, body mass index; BUN, blood urea nitrogen; CIMT, carotid intima media thickness; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DM, diabetes mellitus; ED, erectile dysfunction; FBG, fasting blood glucose; HgA1c, hemoglobin A1c; HT, hypertension; IIEF-5, International Index of Erectile Function-5.

smooth muscle relaxation, and increase arterial blood flow, resulting in erection. However, 35%–40% of patients with ED do not respond to PDE5-Is.<sup>15,22</sup> Administration of a single dose, the use of an inadequate dose, and the lack of dose regulation are the main reasons for nonresponse to PDE5-Is, and approximately 70% of patients do not benefit from this therapy even after rational use.<sup>23,24</sup>

Many studies have shown the relationship between cardiovascular diseases and ED. In a study by Greenstein et al., it was found that there was a correlation between multiple vessel involvement and severe ED in patients undergoing coronary angiography, and a significant correlation between the severity of coronary artery disease and the incidence and severity of ED.<sup>25</sup> In a study by Montorsi et al., the rate of severe ED was found to be higher in men with multivessel involvement in coronary angiography than men with single-vessel involvement.<sup>26</sup> In another study, coronary artery calcifications were evaluated using multidetector computed tomography, and a significant correlation was found between high calcification scores and ED grades determined by the IIEF-5 questionnaire.<sup>27</sup> The coexistence of ED and cardiovascular diseases suggests that both diseases are based on the same basic pathophysiological mechanisms and that atherosclerosis plays a very important role in their formation. The most important change in the early period of atherosclerosis is the increase in arterial intima-media thickness, which can be seen in both the coronary and peripheral arteries. Examining the carotid artery using ultrasound can provide an idea about atherosclerosis.<sup>28,29</sup> Many studies reported in the literature support the coexistence of a thickened carotid intima media and ED. In a study by El Mulla et al., CIMT was significantly higher in the ED group, and a cutoff value >0.90 mm was associated with a higher probability of ED.<sup>30</sup> Zhang et al. showed that CIMT was significantly higher in ED groups, especially among patients with severe ED, and that CIMT was negatively correlated with the IIEF-5 score.<sup>31</sup> Bocchio et al. emphasized that in men without clinical signs of vascular

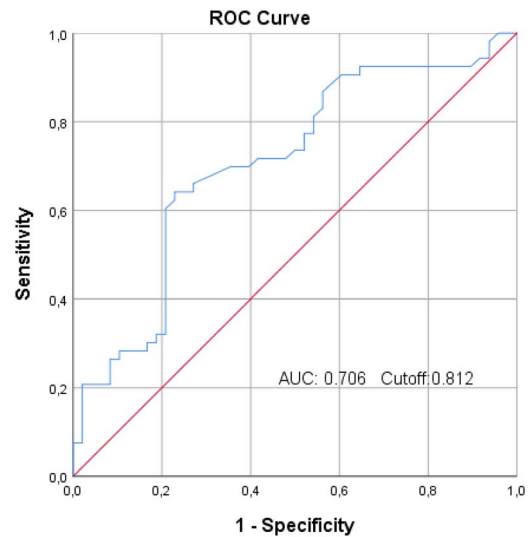
disease, the severity of ED determined by IIEF-5 correlated with CIMT and that CIMT could be used to predict severe ED.<sup>10</sup> In another study, it was shown that there was a positive linear relationship between the degree of ED and the thickness of the carotid intima media.<sup>32</sup> Consistent with the literature, in the current study, CIMT was significantly higher in patients with ED than the control group ( $P < .001$ ). When the patient subgroup analysis was performed, the only significant difference was observed in CIMT, and there was an inverse correlation between the IIEF-5 score and CIMT.

Today, urologists lack a parameter that can predict whether patients with ED will benefit from oral drugs. Such a parameter will reduce both unnecessary drug use and a significant economic burden. In a study by Gamidov et al., a postcompression increase in cavernous artery diameter after the intake of vardenafil was found to be associated with a response to medication. Patients with a  $\geq 50\%$  increase in cavernous artery diameter had the highest response to this drug therapy.<sup>33</sup> In another study, the measurement of bulbocavernosus reflex latency (BCRL) and amplitude (BCRA) to predict the response of sildenafil was evaluated in patients who underwent bilateral nerve-sparing radical prostatectomy. While patients with normal BCRL and BCRA responded to medication, those with prolonged BCRL and low BCRA failed the sildenafil trials.<sup>34</sup> Pelit et al. considered that CIMT, which is an easily measured and inexpensive parameter with proven success, could also be used as a predictor of response to tadalafil. Patients who did not respond to tadalafil had a significantly increased CIMT compared to patients who responded to this therapy, and 90% of patients who had a CIMT greater than 0.67 mm did not respond to tadalafil. However, the authors did not perform a subgroup evaluation of patients with ED.<sup>16</sup> In our study, consistently with previous research, the nonresponders had increased CIMT. As expected, most of our patients with severe ED did not respond to medication, while most patients with mild cases did respond to drug therapy. However, there was no significant difference

**Table 4.** Comparison of CIMT values between responders and nonresponders in all patients with ED and according to ED subgroups.

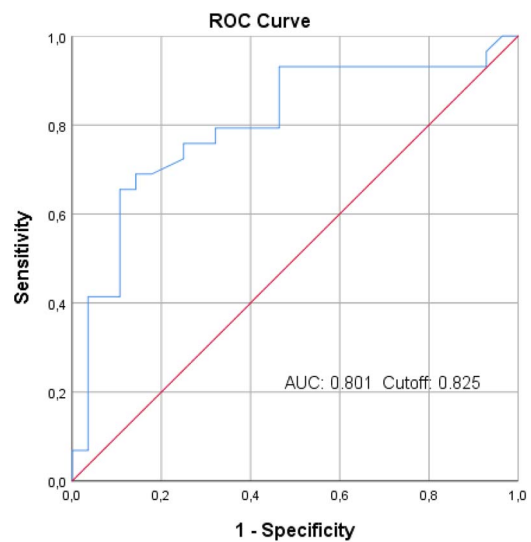
	Severe ED group (n = 42)			Moderate ED group (n = 45)			Mild-moderate ED group (n = 39)			Mild ED group (n = 24)			All patients with ED (n = 150)		
	R (n = 15)	NR (n = 27)	P*	R (n = 27)	NR (n = 18)	P*	R (n = 27)	NR (n = 12)	P*	R (n = 18)	NR (n = 6)	P*	R (n = 87)	NR (n = 63)	P*
CIMT	0.87 ± 0.13	0.86 ± 0.14	.756	0.75 ± 0.13	0.90 ± 0.13	.004	0.70 ± 0.07	0.87 ± 0.20	.008	0.72 ± 0.09	0.72 ± 0.08	.942	0.75 ± 0.12	0.86 ± 0.16	.001
Pretreatment IIEF-5	5.80 ± 0.91	6.11 ± 0.75		9.40 ± 1.24	9.75 ± 1.06		13.85 ± 1.63	14.15 ± 1.28		18.70 ± 1.10	17.67 ± 0.81		11.79 ± 4.71	10.49 ± 4.13	
Post-treatment IIEF-5	13.9 ± 1.1	6.11 ± 0.75		17.13 ± 0.74	9.81 ± 1.08		20.85 ± 1.40	14.1 ± 1.28		23.10 ± 0.31	17.67 ± 0.81		18.71 ± 3.47	10.51 ± 4.21	
P**	<0.001			<0.001			<0.001			<0.001			<0.001		

\*Comparison of CIMT. \*\*Comparison of pretreatment and post-treatment IIEF-5 scores. Abbreviations: CIMT, carotid intima media thickness; ED, erectile dysfunction; IIEF-5, International Index of Erectile Function-5; NR, nonresponder; R, responder.



Diagonal segments are produced by ties.

**Figure 2.** Area under the curve of CIMT for the prediction of response to medication in all patients with ED. Abbreviations: CIMT, carotid artery intima-media thickness; ED, erectile dysfunction.



Diagonal segments are produced by ties.

**Figure 3.** Area under the curve of CIMT for the prediction of response to medication among patients with moderate/mild-moderate ED. CIMT, carotid artery intima-media thickness; ED, erectile dysfunction.

in CIMT between responders and nonresponders in these subgroups. We found that the use of CIMT as a predictor of medication response in patients with moderate/mild-moderate ED was more effective and that at a cutoff value of 0.825 mm, CIMT could serve as a good predictor of these cases, with 65% sensitivity and 89% specificity. We consider that such a predictor maybe useful in assisting the physician in making decisions and informing the patient about the possibility of drug failure. Intracavernosal injections may be considered the first-line treatment for these patients. A verified cutoff value for CIMT can eliminate unnecessary treatments and reduce the related economic burden.

There are three main limitations to our study. First, the number of the participants was low. Second, ultrasound is a



relatively subjective method, and third, all measurements were made by the same radiologist in this study.

## Conclusion

In this study we determined that CIMT is associated with the severity of ED, and increased CIMT may be associated with poor response to PDE5-Is in patients with ED. We determined that the predictive ability of CIMT was higher in patients with moderate/mild-moderate ED. There is a need for further studies with a larger number of patients to validate our results.

## Funding

None declared.

*Conflict of Interest:* None declared.

## Data Availability

The data sets generated and analyzed during the current study are available from the corresponding author on reasonable request.

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