The Relationship Between Levels of Sex Steroids and Coronary Collateral Circulation in Men Patients with Coronary Artery Disease

Aslan Erdoğan[1](İD), Ender Özgün Çakmak[2](İD), Ahmet Güler[1](İD), Alev Kılıçgedik[2](İD), Cevat Kırma[2](İD)

[1] Clinic of Cardiology, Çam and Sakura City Hospital, İstanbul, Turkey
[2] Clinic of Cardiology, Kartal Koşuyolu Training and Research Hospital, İstanbul, Turkey

ABSTRACT

Introduction: Coronary collateral circulation (CCC) is a natural bypass system for restoring blood flow, and a well-developed CCC is held to protect myocardial function and improve survival after coronary obstruction in patients with coronary artery disease (CAD). Sex steroids have been suggested as potentially hampering the course of CAD progression. We explored the relationship between the serum levels of sex steroids and CCC.

Patients and Methods: A total of 115 males with chronic coronary artery disease who had at least one total coronary artery occlusion were included. Patients were divided into two groups: a well CCC group (Rentrop grades 2-3, n= 64) and a poorly developed CCC group (Rentrop grades 0-1, n= 51). Serum levels of total testosterone, free testosterone, sex hormone-binding globulin (SHBG), and dehydroepiandrosterone sulfate (DHEA-S) were recorded. A p-value below 0.05 was accepted as significant in all analyses. The confidence interval was accepted as 95%.

Results: Serum total testosterone (ng/dL; 274.5 ± 57.7 vs. 329 ± 64.8, p< 0.001), free testosterone (pg/mL; 8.2 ± 2.4 vs. 12 ± 3.2, p< 0.001), DHEAS [μg/dL; 111 (58) vs. 160 (85.5), p< 0.001] and SHBG concentrations (nmol/L; 29.3 ± 8.6 vs. 33.2 ± 10.2; p= 0.027) were significantly higher in the well coronary collateral group (WCG). According to the results of multiple regression analyses, diabetes [OR= 3.56, CI (1.26-3.5) p= 0.017], free testosterone level [OR= 1.57, CI (1.26-1.96), p< 0.001] and total testosterone level [OR= 1.01, CI (1.00-1.02), p= 0.009] were determined to be independent predictors.

Conclusion: This study showed that a high level of sex steroids was a predictor of good collateral development in patients with chronic CAD.

Key Words: Coronary artery disease; collateral circulation; sex steroid hormones

Koroner Arter Hastalığı Olan Erkek Hastalarda Koroner Kollateral Dolaşım ile Seks Steroidleri Arasındaki İlişki

ÖZET

Giriş: Koroner kollateral dolaşım, koroner arter oklüzyonunda kan akımının devamlılığını sağlayarak miyokard fonksiyonlarını koruyan ve sağkalımı arttıran doğal bypass sistemidir. Seks steroidlerinin de koroner arter hastalığının ilerlemesine karşı potansiyel olarak koruyucu bir role sahip olduğu gösterilmiştir. Bu çalışmada koroner kollateral dolaşım ile seks steroidleri arasındaki ilişkiyi araştırmayı amaçladık.

Hastalar ve Yöntem: En az bir damarında kronik total okluzyon olan 115 erkek stabil koroner arter hastası çalışmaya dahil edildi. Hastalar iyi gelişmiş koroner kollateral dolaşım (Rentrop derece 2-3, n= 64) ve kötü kollateral dolaşım (Rentrop derece 1-2, n= 51) olarak iki gruba ayrıldı. Serum total testosteron, serbest testosteron, seks hormon-bağlayıcı globulin (SHBG) and dehidroepiandrosteron sulfat (DHEA-S) düzeyleri ölçülüp kaydedildi.

Bulgular: Serum total testosteron (ng/dL; 274.5 ± 57.7 vs. 329 ± 64.8, p< 0.001), serbest testosteron (pg/mL; 8.2 ± 2.4 vs. 12 ± 3.2, p< 0.001), DHEAS [μg/dL; 111 (58) vs. 160 (85.5), p< 0.001], and SHBG konsantrasyonları (nmol/L; 29.3 ± 8.6 vs. 33.2 ± 10.2; p= 0.027) iyi gelişmiş kollateral dolaşım grubunda anlamlı düzeyde yüksek saptandı. Multiple regresyon analizinde de serbest testosteron [OR= 0.57, CI (0.44-0.74), p< 0.001], ve SHBG [OR= 0.91, CI (0.84-0.99), p= 0.022] düzeyinin iyi kollateral dolaşımın bağımsız öngörücüsü olduğu saptandı. Tüm analizlerde 0.05'in altındaki p değeri anlamlı kabul edildi. Güven aralığı %95 olarak alındı.

Sonuç: Bu çalışma, yüksek düzeyde seks steroidlerinin kronik KAH'lı hastalarda iyi kollateral gelişimin bir göstergesi olduğunu göstermiştir.

Anahtar Kelimeler: Koroner arter hastalığı; kollateral dolaşım; seks steroid hormonlar

Cite this article as: *Erdoğan A, Çakmak EÖ, Güler A, Kılıçgedik A, Kırma C. The relationship between levels of sex steroids and coronary collateral circulation in men patients with coronary artery disease. Koşuyolu Heart J 2022;25(1):33-9.*

Correspondence

Aslan Erdoğan

E-mail: aslanerdogan2011@hotmail.com
Submitted: 15.07.2021
Accepted: 27.01.2022
Available Online Date: 15.04.2022

INTRODUCTION

Coronary artery disease (CAD) remains the most significant contributor to cardiovascular disease-related mortality, despite advances in diagnostic and therapeutic methods in the past few decades[1-3]. Accordingly, the association of non-traditional risk factors with CAD has become increasingly studied in the past few decades with the emergence of several potential non-traditional risk factors[4,5]. Based on hypotheses linking androgen deficiency to an increased risk of CAD, the role of androgens in cardiovascular diseases has become a popular research area,[3-6] and testosterone has been suggested to play a potentially protective role against the development and progression of CAD[7,8].

Coronary collateral circulation (CCC) is a natural bypass system for restoring blood flow in the myocardium in cases of stenosis or occlusion of a coronary vessel, while a well-developed CCC is considered to protect myocardial function and improve survival after coronary obstruction in patients with CAD[9]. The identification of factors associated with the development of CCC is of great clinical significance, although the exact mechanism of the development of good CCC has not yet been elucidated[10].

Prospective studies have shown an inverse correlation between testosterone levels and the incidence of CAD[11,12]. Data from epidemiological statistics have indicated decreased serum testosterone levels in parallel with the occurrence of age-related diseases such as premature CAD in men[13] and adverse cardiovascular outcomes including a higher incidence of CAD and a high cardiometabolic profile (increased blood pressure, insulin resistance, dyslipidaemia, atherosclerosis, thrombosis) [14,15]. Similarly, sex hormone-binding globulin (SHBG), a key protein involved in testosterone bioavailability, has been reported to be associated with prevalent metabolic disease in men[16].

There are publications in the literature demonstrating that androgens contribute to angiogenesis, which is considered one of the main mechanisms of CCC, at the microvascular level through the androgen receptor[17]. Moreover, it has been proposed that androgens can activate vascular repair and neovascularisation[18].

Although significant studies have been conducted on the relationship of androgens with CAD and neovascularisation,[11,17,18] studies on androgens and CCC are limited. In this study, we aimed to investigate the relationship between androgens and CCC in male patients with coronary artery occlusion, which plays a crucial role in the prevention of cardiovascular mortality and morbidity.

PATIENTS and METHODS

Study Population

A total of 129 patients attending our clinic between June 2019 and March 2020 were included. These patients had at least one coronary total occlusion in coronary angiography and verified myocardial ischaemia in treadmill exercise tests or myocardial perfusion scintigraphy. Patients with acute coronary syndrome diagnosed within the previous 30 days, a previous history of coronary bypass surgery, stent restenosis, heart failure (left ventricular ejection fraction< 40%), chronic kidney disease (GFR< 90 mL/min/1.73 m^2), receiving hormone therapy and active malignancy or endocrine disorder were excluded from the study. Of the 129 patients, 14 were excluded since they did not meet the inclusion criteria, and finally, the study was conducted with the remaining 115 patients. Patients were divided into two groups: the well collateral flow (WCF) group (Rentrop grades 2-3, n= 61) and the poor collateral flow group (PCF; Rentrop grades 0-1, n= 54) according to the Rentrop Cohen classification[19]. Before the beginning, the study's protocol was approved by the institutional review board (IRB) ethics committee. The patients were informed about the objectives and protocol of the study in detail and gave informed written consent. The study was conducted under the Declaration of Helsinki.

Study Parameters

Patients' age, smoking status, comorbidities (diabetes mellitus, hypertension), family history of CAD, anthropometrics [body mass index (BMI, kg/m^2), hip circumference, and waist circumference], and sex steroids [total testosterone, free testosterone, SHBG and dehydroepiandrosterone sulfate (DHEA-S)] were recorded and compared the well CCC and poor CCC groups.

Coronary Angiography and Coronary Collateral Circulation

Coronary angiography was performed with the Judkins technique using an angiography device (Siemens Artis zee Medical Systems). The angiography results of the patients were evaluated by two experienced interventional cardiologists who were blind to the study. According to the Judkins classification, Rentop grades were defined as follows: Rentrop 0= no filling in any collateral vessel; Rentrop 1= impoverished collateral flow, but no filling of epicardial arteries; Rentrop 2= partial perfusion, epicardial arteries receive a contrast agent, but no complete filling; and Rentrop 3= complete perfusion. The contrast agent completely fills epicardial vessels. Based on the Rentrop classifications, grades 0 and 1 were considered poor coronary collateral development, and grades 2 and 3 were considered poor coronary collateral development[19].

Laboratory Analysis

Peripheral venous blood samples were collected following a 12-hour fast for complete blood count and measurements of biochemical parameters and androgen levels.

Serum levels of total testosterone (normal range= 175-781 ng/dL), free testosterone (normal range= 0.70-21.45 pg/mL), DHEA-S (normal range= 5-253 μg/dL), and SHBG (13.5 nmol/L) were measured via the analysis of 8-10 cc serum samples collected after an overnight fast in a central laboratory using the radioimmunoassay method.

Statistical Analysis

The data were presented as mean ± SD or median [IQR] for continuous variables and percentage (n) for categorical variables. The Kolmogorov-Smirnov test searched for the normal distribution of continuous variables. The participants were allocated to two distinct groups according to Rentrop grades. The quality of the collateral flow to 100 occluding coronary arteries was accepted as good for Rentrop grade 2 or 3 and poor for grade 0 or 1. The normally and non-normally distributed continuous variables were compared using a students' t-test and Mann-Whitney U test, respectively. The frequency of categorical variables in these groups was compared with the Chi-square test. A logistic regression analysis was additionally performed to identify the determinants of well collateral flow. The parameters distinguishing the groups at a significant level (presence of DM, smoking status, serum-free testosterone, total testosterone, and DHEAS levels) were included in binary and multiple regression analyses. The confidence interval was accepted as 95%. Since age is an established determinant of total and free testosterone levels, it was included in the regression analysis as a constant variable. Finally, the predictive performance of serum-free testosterone and total testosterone levels was determined by ROC analysis. A p-value below 0.05 was accepted as significant in all analyses. The Statistical Package for the Social Sciences (SPSS Version 22.0, SPSS Inc., Chicago, IL, USA) was used for these assessments.

RESULTS

When the patients were grouped according to the quality of collateral flow, Group PCF involved 54 individuals, and Group WCF involved 61.

The frequency of diabetics and smokers was higher in the poor collateral circulation group (63.9% vs. 48.7%, 62.3% vs. 51.3%). The remaining demographic, clinical, and angiographic features were comparable (Table 1).

Among the entire set of laboratory parameters, serum total testosterone (ng/dL; 274.5 ± 57.7 vs. 329 ± 64.8, p< 0.001), free testosterone (pg/mL; 8.2 ± 2.4 vs. 12 ± 3.2, p< 0.001), DHEAS [μg/dL; 111 (58) vs. 160 (85.5), p< 0.001] and SHBG concentrations (nmol/L; 29.3 ± 8.6 vs. 33.2 ± 10.2; p= 0.027) were significantly higher in the WCF group (Table 2).

Binary logistic regression analysis showed that DM, smoking status, total testosterone, free testosterone, and DHEAS level could be potential predictors of good collateral flow. According to multiple logistic regression analyses, DM [OR=

Table 1. Demographics of the study population

	Overall (n= 115)	Group PCF (n= 54)	Group WCF (n= 61)	p
Age, years; Mean ± SD[1]	58.3 ± 7.3	57.2 ± 7	59.3 ± 7.5	0.119
Hip circumference, cm; Mean ± SD[1]	101.7 ± 9.1	103 ± 8.8	100.5 ± 9.4	0.145
Waist circumference, cm; Mean ± SD[1]	101.7 ± 9.1	100.8 ± 11.6	100.6 ± 9.9	0.920
BMI, kg/m^2; Median (IQR)[2]	28.4 (3)	28.5 (5.4)	28.3 (2.5)	0.349
Total occlusion; %(n)[3]				
LAD	33 (38)	33.3 (18)	32.8 (20)	0.690
Cx	17.4 (20)	20.4 (11)	14.8 (9)	
RCA	49.6 (57)	46.3 (25)	52.5 (32)	
Diabetes mellitus; %(n)[3]	48.7 (56)	63.9 (39)	31.5 (17)	0.001
Hypertension; %(n)[3]	41.7 (48)	38.9 (21)	44.3 (27)	0.560
Smoking; %(n)[3]	51.3 (59)	62.3 (38)	38.9 (21)	0.012
Family history of CVD; %(n)[3]	48.7 (56)	51.9 (28)	45.9 (28)	0.524

1: Students' t-test was used for comparison, 2: Mann-Whitney U test was used for comparison, 3: Chi-square test was used for comparison, BMI: Body mass index, Cx: Circumflex artery, CVD: Cardiovascular disease, IQR: Interquartile range, LAD: Left anterior descending artery, RCA: Right coronary artery, SD: Standard deviation, PCF: Poor collateral function, WCF: Well collateral function.

Table 2. Laboratory tests of the study population

	Group PCF (n= 54)	Group WCF (n= 61)	p
Creatinine, mg/dL; Median (IQR)[1]	0.91 (0.19)	0.92 (0.19)	0.567
Total cholesterol, mg/dL; Mean ± SD[2]	222.3 ± 36	219.6 ± 41.4	0.711
LDL-cholesterol, mg/dL; Median (IQR)[1]	123 (53)	110 (53)	0.726
HDL-cholesterol, mg/dL; Median (IQR)[1]	48 (12)	46 (12)	0.378
Triglyceride, mg/dL; Median (QR)[1]	230 (331)	230 (150)	0.855
Hemoglobin, g/dL; Median (QR)[1]	13.4 (2.1)	13.1 (2)	0.195
Leukocyte count, *1000/dL; Median (QR)[2]	7.8 ± 1.1	7.9 ± 1	0.610
Platelet count, *1000/dL; Median (QR)[1]	289 (189)	246 (215)	0.295
LVEF; %; Median (QR)[1]			0.427
Total testosterone, ng/dL; Mean ± SD[2]	274.5 ± 57.7	329 ± 64.8	<0.001
Free testosterone, pg/mL; Mean ± SD[2]	8.2 ± 2.4	12 ± 3.2	<0.001
DHEAS, μg/dL; Median (QR)[1]	111 (58)	160 (85.5)	<0.001
SHBG, nmol/L; Mean ± SD[2]	29.3 ± 8.6	33.2 ± 10.2	0.027

1 Mann-Whitney-U test was used for comparison, 2 Students' t-test was used for comparison. DHEAS: Dehydroepiandrosterone sulfate, IQR: Interquartile range, LVEF: Left ventricular ejection fraction, SHBG: Sex-hormone-binding globuline, PCF: Poor collateral function, WCF: Well collateral function.

Table 3. Results of the binary and multiple regression analyses performed for identifying the variables that may anticipate the presence of good collateral flow

	OR	CI 95%	p
Binary Logistic Regression Analysis			
Diabetes Mellitus	0.26	0.12-0.56	0.001
Smoking	0.39	0.18-0.82	0.013
Total testosterone	1.02	1.01-1.02	<0.001
Free testosterone	1.62	1.34-1.96	<0.001
DHEAS	1.01	1.00-1.02	0.003
SHBG	1.05	1.00-1.09	0.031
Multiple Logistic Regression Analysis			
Age	0.98	0.91-1.05	0.505
Diabetes Mellitus	0.22	0.07-0.69	0.009
Smoking	0.27	0.08-0.90	0.032
Total testosterone	1.00	0.99-1.01	0.304
Free testosterone	0.57	0.44-0.74	<0.001
DHEAS	0.99	0.99-1.00	0.078
SHBG	0.91	0.84-0.99	0.022

CI: Confidence interval, DHEAS: Dehydroepiandrosterone sulfate, OR: Odds ratio, SHBG: Sex-hormone-binding globuline, PCF: Poor collateral function, WCF: Well collateral function.

3.56, CI (1.26-3.5), p= 0.017], free testosterone level [OR= 0.57, CI (0.44-0.74), p< 0.001] and total testosterone [OR= 1.01, CI (1.00-1.02), p= 0.009] were determined as independent predictors (Table 3).

ROC analysis was performed to evaluate the predictive performance of total testosterone and free testosterone levels to estimate well collateral flow. The AUCs for these parameters were 0.75 and 0.82, respectively (Figure 1). The cut-off value

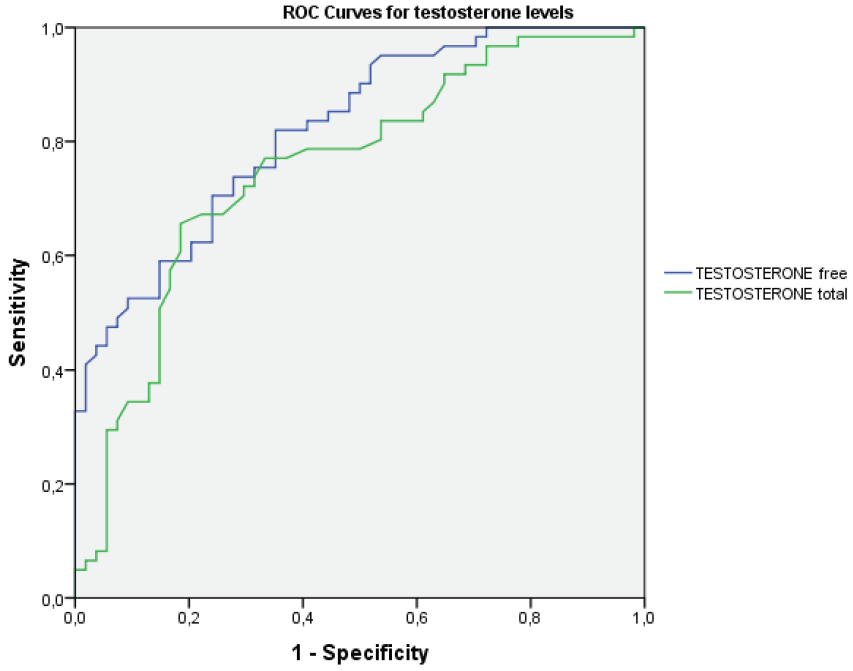

Figure 1. ROC curves for testosterone levels.

of total testosterone was detected as 291 ng/dL with a sensitivity of 72% and a specificity of 70% (p< 0.01), while that of free testosterone was 9.7 pg/mL (74% sensitivity and 72% specificity, p< 0.01).

DISCUSSION

In this study, we observed higher levels of free testosterone and total testosterone in patients with well collateral circulation compared to those with poor collateral circulation. In the multivariate regression analysis, a low level of free testosterone and total testosterone was found to be a predictor of poor collateral circulation.

There are two distinct adaptation mechanisms in the development of coronary collateral vessels in the human heart: angiogenesis and arteriogenesis[20]. Arteriogenesis is the opening of pre-existing and closed anastomotic canals because of the pressure gradient, which develops following coronary stenosis or occlusion, allowing flow[21,22]. Angiogenesis is the formation of new vessels after the activation of endothelial cells by cytokines released from myocardial cells destroyed by coronary ischaemia or necrosis[21-23].

Numerous *in vivo* and *in vitro studies* have shown that androgens contribute to angiogenesis by transcriptionally controlling the target genes through androgen receptors and by increasing the interaction of multiple signaling pathways[17,18]. Simultaneously, studies that have shown that androgens increase arterial blood flow causing vascular vasodilatation have proposed that androgens may contribute to angiogenesis, which is one of the fundamental mechanisms of coronary collateral circulation (CCC)[24,25].

Previous studies have found a negative correlation between serum total testosterone, free testosterone levels, and CAD, and a low androgen level was an important marker of the severity of CAD[26]. The authors also noted a positive correlation between serum total, free and bioavailable testosterone levels and flow-mediated dilation of the brachial artery (FMD) as an indicator of endothelial function[24,25].

In addition, it has been emphasised that testosterone and SHBG levels are inversely related to cardiovascular events, and a high testosterone level is a specific marker for predicting reduced cardiovascular events[11,13,14].

Although the exact mechanisms underlying the association between serum testosterone levels and CAD have not been fully elucidated, it has been considered that the abnormal activation of an inflammatory response, accelerated atherosclerosis and vasomotor and endothelial dysfunction are likely to be involved as part of a complex interconnected process[14,17,24,25].

The present study revealed that low serum sex steroid levels increased the probability of poor CCC in male patients with coronary occlusion, while sensitivity analyses indicated free testosterone levels as the most important sex steroid in predicting the development of poor CCC. This seems remarkable, given the relationship between the physiological concentration of intracoronary testosterone and epicardial coronary artery dilatation, increased volumetric blood flow in men with CAD, and

the positive effects of short- or long-term testosterone therapy on coronary and peripheral vasomotion[24-27].

Diabetes mellitus was also determined as a significant risk factor for coronary occlusion as well as the development of poor CCC in patients with coronary occlusion in our cohort. The association of diabetes with an increased risk of poor collateral development in patients with coronary occlusion also has been reported in previous studies[28]. Similarly, our findings revealed an association of diabetes with poor CCC.

The potential lack of generalisability and failure to achieve statistical significance in some parameters due to the relatively small number of cases and sample size may be seen as the main limitations of this study.

In conclusion, in this study, a low androgen level was found to be a risk factor for poor collateral development. In addition, sensitivity analyses revealed that free testosterone and total testosterone were effective in predicting poor CCC development.

Ethics Committee Approval: The approval for this study obtained from Yüzüncü Yıl University Faculty of Medicine Clinical Researches Ethics Committee (Decision No: 07, Date: 29.05.2019).

Informed Consent: This is retrospective study, we could not obtain written informed consent from the participants.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept/Design - ÖÇ; Analysis/Interpretation - AG; Data Collection - MK, SB; Writing - AE; Critical Revision - AK; Final Approval - CK; Statistical Analysis - MO; Overall Responsibility - AE.

Conflict of Interest: The authors declared that there was no conflict of interest during the preparation and publication of this article.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Lippi G, Franchini M, Cervellin G. Diagnosis and management of ischemic heart disease. Semin Thromb Hemost 2013;39:202-13. [Crossref]
2. Murray CJ, Lopez AD. Mortality by cause for eight regions of the world: global burden of disease study. Lancet 1997;349:1269-76. [Crossref]
3. Allameh F, Pourmand G, Bozorgi A, Nekuie S, Namdari F. The association between androgenic hormone levels and the risk of developing coronary artery disease (CAD). Iran J Public Health 2016;45:14-9.
4. Balagopal PB, de Ferranti SD, Cook S, Daniels SR, Gidding SS, Hayman LL, et al. Nontraditional risk factors and biomarkers for cardiovascular disease: mechanistic, research, and clinical considerations for youth: a scientific statement from the American Heart Association. Circulation 2011;123:2749-69. 4 [Crossref]
5. Gururani K, Jose J, George PV. Testosterone as a marker of coronary artery disease severity in middle aged males. Indian Heart J 2016;68(Suppl 3):16-20. [Crossref]
6. Rohrmann S, Platz EA, Selvin E, et al. The prevalence of low sex steroid hormone concentrations in men in the Third National Health and Nutrition Examination Survey (Nhanes III). Clin Endocrinol 2011;75:232-9. [Crossref]
7. Empen K, Lorbeer R, Dörr M, Haring R, Nauck M, Gläser S et al. Association of testosterone levels with endothelial function in men: results from a population-based study. Arterioscler Thromb Vasc Biol 2012;32:481-6. [Crossref]
8. Akishita M, Hashimoto M, Ohike Y, Ogawa S, Iijima K, Eto M, et al. Low testosterone level is an independent determinant of endothelial dysfunction in men. Hypertens Res 2007;30:1029-34. [Crossref]
9. Mokarrab MI, Mostafa M, Khamis A, Abdul-Wahab SA, Yousef MG. Effect of collateral circulation on left ventricular systolic function in patients with totally occluded artery undergoing PCI. Egypt J Hosp Med 2019;74(7):1636-42. [Crossref]
10. İleri M, Güray Ü, Yetkin E, Gürsoy HT, Bayır PT, Şahin D, et al. A new risk scoring model for prediction of poor coronary collateral circulation in acute non-ST-elevation myocardial infarction. Cardiol J 2016;23(1):7. [Crossref]
11. Haring R, Völzke H, Steveling A, Krebs A, Felix SB, Schöfl C, et al. Low serum testosterone levels are associated with increased risk of mortality in a population-based cohort of men aged 20-79. Eur Heart J 2010;31:1494-501. [Crossref]
12. Alkamel A, Shafiee A, Jalali A, Boroumand M, Nozari Y. The association between premature coronary artery disease and level of testosterone in young adult males. Arch Iran Med 2014;17:545-50.
13. Hu X, Rui L, Zhu T, Xia H, Yang X, Wang X et al. Low testosterone level in middle-aged male patients with coronary artery disease. Eur J Intern Med 2011;22:133-6. [Crossref]
14. Kirby M, Hackett G, Ramachandran S. Testosterone and the Heart. Eur Cardiol Rev 2019;14(2):103-10. [Crossref]
15. Yeap BB, Alfonso H, Chubb SA, Handelsman DJ, Hankey GJ, Almeida OP et al. In older men an optimal plasma testosterone is associated with reduced all-cause mortality and higher dihydrotestosterone with reduced ischemic heart disease mortality, while estradiol levels do not predict mortality. J Clin Endocrinol Metab 2014;99:9-18. [Crossref]
16. Sarkar M, VanWagner LB, Terry JG, Carr JJ, Rinella M, Schreiner PJ et al. Coronary artery risk development in young adults (CARDIA) cohort. Sex hormone-binding globulin gevels in young men are associated with nonalcoholic fatty liver disease in midlife. Am J Gastroenterol 2019,114(5),758-763. [Crossref]
17. Sieveking DP, Lim P, Chow RW, Dunn LL, Bao S, McGrath KC, et al. A sex-specific role for androgens in angiogenesis. J Exp Med 2010;207:345-52. [Crossref]
18. Lam YT, Lecce L, Tan JT, Bursill CA, Handelsman DJ, Ng MK. Androgen receptor mediated genomic androgen action augments ischemia neovascularization. Endocrinology, 2016;157:4853-64. [Crossref]
19. Rentrop KP, Cohen M, Blanke H, Phillips RA. Changes in collateral channel filling immediately after controlled coronary artery occlusion by an angioplasty balloon in human subjects. J Am Coll Cardiol 1985;5:587-92. [Crossref]
20. Altman JD, Bache RJ. The coronary collateral circulation. ACC Current J Review 1997;17-21. [Crossref]
21. Conway EM, Collen D, Carmeliet P. Moleculer mechanisms of blood vessel growth. Cardiovasc Res 2001;49:507-21. [Crossref]
22. Schaper W. Tangential wall stress as a molding force in the development of collateral vessels in the canine heart. Experientia 1967;23:595-6. [Crossref]
23. van der Zee R, Murohara T, Luo Z, Zollmann F, Passeri J, Lekutat C, et al. Vascular endothelial growth factor/ vascular permeability factor augments nitric oxide release from quinescent rabbit and human vascular endothelium. Circulation 1997;95:1030. [Crossref]
24. Webb CM, McNeill JG, Hayward CS, de Zeigler D, Collins P. Effects of testosterone on coronary vasomotor regulation in men with coronary heart disease. Circulation 1999;100:1690-6. [Crossref]

25. Ong PJ, Patrizi G, Chong WC, Webb CM, Hayward CS, Collins P. Testosterone enhances flow-mediated brachial artery reactivity in men with coronary artery disease. Am J Cardiol 2000;85:269-72. [Crossref]

26. Gururani K, Jose J, George PV. Testosterone as a marker of coronary artery disease severity in middle aged males. Indian Heart J 2016;68(Suppl 3):16-20. [Crossref]

27. Webb CM, Elkington AG, Kraidly MM, Keenan N, Pennell DJ, Collins P. Effects of oral testosterone treatment on myocardial perfusion and vascular function in men with low plasma testosterone and coronary heart disease. Am J Cardiol 2008;101:618-24. [Crossref]

28. Abaci A, Oğuzhan A, Kahraman S, Eryol NK, Unal S, Arinç H, et al. Effect of diabetes mellitus on formation of coronary collateral vessels. Circulation 1999;99:2239-42. [Crossref]