ORIGINAL ARTICLE

Eastern Journal of Medicine

East J Med 29(4): 455-461, 2024
DOI: 10.5505/ejm.2024.25478

Evaluation of the Relationship Between the Degree of Coronary Collateral Circulation and Levels of Androgens in Male Patients with Coronary Artery Disease

Aslan Erdoğan[1*], Ender Özgün Çakmak[2], Ahmet Karaduman[3], Ahmet Güler[1], Cevat Kirma[3]

[1]Department of Cardiology,Cam & Sakura City Hospital
[2]Department of Cardiology, Acıbadem Maslak, Hospital
[3]Department of Cardiology, Kartal Kosuyolu Training and Research Hospital, Istanbul

ABSTRACT

Coronary collateral circulation (CCC) comprises vascular pathways that activate in severe coronary stenosis to preserve perfusion. This study investigates the relationship between CCC development and male sex steroids.

A retrospective analysis was performed on 149 male patients with ≥ 95% stenosis in epicardial coronary arteries and 29 with normal coronaries, identified via coronary angiography between January 2017 and December 2023. The cohort included 29 control patients, 99 with well collateral flow (WCF), and 50 with poor collateral flow (PCF). Serum levels of total testosterone, free testosterone, dehydroepiandrosterone sulfate (DHEA-S), and sex hormone-binding globulin (SHBG) were measured. Ordinal and logistic regression was used to analyze the relationship between sex steroid levels and collateral development.

The PCF group exhibited higher rates of diabetes mellitus (p=0.001) and smoking (p<0.001). The WCF group had significantly higher levels of total testosterone (350.6 ± 78.5 vs. 273.8 ± 59.9 ng/dL, p<0.001), free testosterone (12.1 ± 3.3 vs. 7.2 ± 2.0 pg/mL, p<0.001), DHEA-S (180.5 ± 69.5 vs. 131.9 ± 87.9 µg/dL, p<0.001), and SHBG (35.3 ± 11.0 vs. 24.8 ± 6.9 nmol/L, p<0.001). Multiple logistic regression revealed that DM [OR = 1.923, 95% CI (1.041–4.092), p = 0.012] directly predicted PCF, whereas free testosterone [OR = 0.689, 95% CI (0.557–0.851), p < 0.001] and SHBG [OR = 0.903, 95% CI (0.849–0.960), p = 0.001] were inversely predictors.

The study highlights the important role of sex steroids in coronary collateral development, with free testosterone and SHBG as key predictors of CCC levels in men with coronary occlusion.

Keywords: Coronary collateral circulation, dehydroepiandrosterone, sex steroids, testosterone

Introduction

Coronary artery disease (CAD) remains a major contributor to mortality and morbidity on a global scale. (1). However, the cardiac effects of CAD vary among patients, influenced by traditional risk factors and the presence of coronary collaterals (2,3). Coronary collaterals provide an alternative flow path by enlarging in response to the pressure gradient caused by a flow-restricting narrowing in the coronary arteries. Well-developed coronary collateral circulation (CCC) reduces myocardial ischemia, underscoring the importance of investigating these vessels at the molecular level (3,4). This has led to increased research aimed at promoting collateral development when adequate coronary revascularization cannot be achieved medically or invasively.

Collateral development occurs either through angiogenesis, the budding of new capillaries from existing blood vessels following chronic ischemia or hypoxia, or through arteriogenesis, the enlargement and maturation of pre-existing intracoronary anastomoses from birth (5-7). Literature suggests that androgens contribute to angiogenesis, a key mechanism of CCC, at the microvascular level through the androgen receptor (8). Additionally, androgens are proposed to activate vascular repair and neovascularization (9).

While some recent studies have investigated the relationship between coronary collateral development

*Corresponding Author: Aslan Erdoğan, Çam and Sakura Training and Research Hospital, Cardiology, Başakşehir avenue , G-434 Cd., No:22L, 34000 Istanbul, Turkey
E-mail: aslanerdogan2011@hotmail.com, Phone: +90 506 8539783, Fax: +90 212 909 60 00
ORCID ID: Aslan Erdoğan: 0000-0002-1094-5572, **Ender Özgün Çakmak:** 0000-0001-6767-6935, **Ahmet Karaduman:** 0000-0002-4039-1259, **Ahmet Güler:** 0000-0002-0324-1200, **Cevat Kirma:** 0000-0001-9986-050X
Received: 03.08.2024, **Accepted:** 19.09.2024

and sex steroids (8,9), most have concentrated on atherosclerosis (10,11). Testosterone is thought to potentially play a protective role in the development and progression of CAD (12). Several studies have demonstrated an inverse correlation between angiographically confirmed CAD and testosterone levels, with CAD patients exhibiting lower testosterone levels compared to those with normal coronary arteries (13,14). Additionally, low free testosterone levels have been associated with an increased risk of mortality (15). Sex hormone-binding globulin (SHBG), a protein that regulates testosterone bioavailability, is also linked to metabolic effects. Low levels of both testosterone and SHBG have been inversely related to the prevalence of metabolic disease in men (16).

Despite these findings, there is a need for studies specifically explaining the relationship between the degree of CCC and sex steroids. In this study, we aim to contribute to this area of research by clinically investigating the relationship between sex steroids, which have a significant relationship with CAD, and coronary collateral flow.

Materials and Methods

This retrospective, multicenter observational study was conducted at the Department of Cardiology, Kosuyolu Training and Research Hospital, and Cam&Sakura City Hospital. The study included a cohort of 149 consecutive patients with at least one vessel having ≥ 95% critical stenosis and 29 normal coronary who underwent coronary angiography between January 2017 and December 2023. Patients were excluded if they met any of the following criteria: diagnosed with acute coronary syndrome, history of coronary bypass surgery, stent restenosis, undergoing hormone therapy, active cancer, endocrine disorders, left ventricular ejection fraction (LVEF) below 45% as determined by echocardiography, regular hemodialysis therapy, and those with missing data. After these exclusions, the final analysis included a total of 178 subjects.

Demographic, laboratory, and clinical data were collected from the hospital's medical database. This study was conducted following the principles outlined in the Declaration of Helsinki. The study protocol was approved by the ethics committee of Cam&Sakura City Hospital (approval date: 24/07/2024, decision number: 1147).

Definitions and Risk Factors: Before the procedure, detailed baseline laboratory parameters were recorded for each patient. Renal function was evaluated with the validated formula (17). Diabetes mellitus (DM) was identified by fasting glucose levels of 126 mg/dL or higher, postprandial glucose levels of 200 mg/dL or more, or the use of antidiabetic medication (17). Hypertension (HT) was defined as having a systolic blood pressure over 140 mm Hg and/or diastolic blood pressure exceeding 90 mm Hg or being on antihypertensive medication (18). Dyslipidemia was diagnosed according to the following criteria: total cholesterol ≥240 mg/dL, LDL cholesterol ≥130 mg/dL, HDL cholesterol <40 mg/dL for men or <50 mg/dL for women, and triglycerides ≥150 mg/dL (19). Body mass index (BMI) was calculated by dividing the weight in kilograms by the square of the height in meters (kg/m^2). Smoking status was defined as current smoking if a participant smoked regularly or had smoked within the month preceding the study.

Coronary Angiography: Selective coronary angiography was performed on all patients using a 6F diagnostic catheter via the right or left femoral, brachial, or radial artery with the Judkins technique. The angiography devices used were the 'Philips Medical Systems Integris H 5000, Netherlands' and 'Siemens Artis Zee Medical Systeme'. Iopromide (Ultravist-370) or Iohexol (Omnipaque 350 mg/ml) was used as the contrast agent. The coronary arteries were imaged in right and left oblique positions using cranial and caudal angulations. Measurements for all patients were taken at the end of diastole in the position where the coronary lesion was best visualized and caused the greatest lumen narrowing. The angiographic grading of the collaterals supplying the occluded coronary artery was performed according to the Rentrop classification (20).

According to the Rentrop classification: Rentrop 0: No collateral filling, Rentrop 1: very weak collateral flow is observed, but epicardial arteries do not fill, Rentrop 2: partial perfusion; epicardial arteries are opacified but not filled, Rentrop 3: complete perfusion; the contrast medium fills the epicardial vessels. Based on the Rentrop classification, grades 0 and 1 were considered poor collateral development, while grades 2 and 3 were considered good collateral development.

Statistical Analysis: The distribution of the data was assessed using both analytical methods, such as the Kolmogorov–Smirnov test, and visual methods, including histograms and probability plots. Continuous variables were presented as mean ± standard deviation (SD) or median with interquartile range (25th–75th percentiles), while categorical variables were reported as numbers with corresponding percentages. For comparison of continuous variables, one-way analysis of variance (ANOVA) and Kruskal-Wallis tests were employed, depending on data distribution. Categorical variables

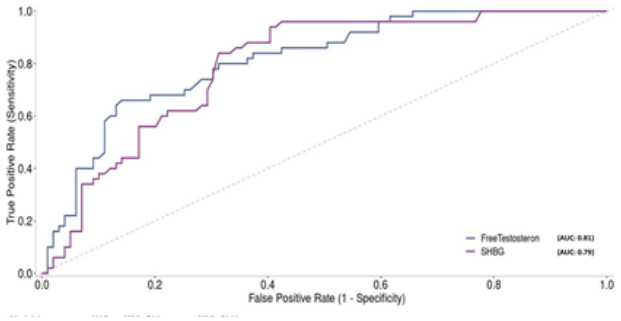

Fig. 1. Receiver operating characteristic (ROC) analysis was performed to compare the discriminatory abilities of free testosterone and SHBG predicting WCF

were compared using Chi-square or Fisher's exact tests. Ordinal logistic regression was used to identify independent predictors of collateral flow compared to the control group. Binary logistic regression was conducted to determine the independent parameters associated with the degree of CCC in the patient population. Receiver operating characteristic (ROC) curve analysis was performed to identify the cut-off value of free testosterone for predicting well coronary flow (WCF) using the Youden index. Pairwise comparison of ROC curves for parameters independently associated with collateral circulation was carried out using the DeLong method. A two-tailed p-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using R statistical software (version 4.3.2, Vienna, Austria)

Results

Baseline Characteristics and Serum Sex Steroid Levels in Study Groups: In the final analysis, the study included 178 participants. The mean age was higher in the WCF group compared to the poor collateral flow (PCF) and control groups [58.9 ± 6.4 vs 57.1 ± 7.8 and 57.2±3.81 $p<0.05$]. The PCF group also showed a statistically higher prevalence of DM (56% vs. 17.2% and 23.2%, $p<0.001$) and smoking (60% vs 24.1% and 28.3%, $p<0.001$) than both control subjects and patients with WCF. Also, patients with PCF had significantly lower values for total testosterone (273.8 ± 59.9 vs 350.6 ± 78.5 and 382±56.8 ng/dL, $p<0.001$), free testosterone (7.2 ± 2.0 vs. 11.6±3.86 and 12.1 ± 3.3 pg/mL, $p<0.001$), dehydroepiandrosterone sulfate (DHEA-S) (131.9 ± 87.9 vs. 180.5 ± 69.5 and 205±72.4 µg/dL, $p<0.001$), and SHBG (24.8±6.9 vs. 34.5±9.2 and 35.3±11.0 nmol/L, $p<0.001$ for each) as compared with both control subjects and patients with WFC. Other factors such as the family history of CAD, BMI, creatinine, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, haemoglobin, leukocyte count, platelet count, and LVEF were similar between the all groups. A detailed overview of the demographic, clinical, and laboratory characteristics by CCC status is provided in Table 1.

Independent Predictors of Well Coronary Collateral Flow in Binary Logistic Regression: We performed ordinal logistic regression analysis as a supplementary sensitivity analysis. Ordinal logistic regression analysis showed that only free testosterone [OR = 0.870, 95% CI (0.794–0.951), p =0.002] and total testosteron [OR = 0.992, 95% CI (0.987–0.997), p=0.002] were independent precitors of well or poor collateral flow compared to control group (Table 2). Additionally, binary logistic regression analysis identified DM, free testosterone, and SHBG levels as potential predictors of collateral flow in patient group. Multiple logistic regression analysis showed that DM [OR = 1.923, 95% CI (1.041–4.092), p = 0.012] was directly associated with PCF, whereas free testosterone levels [OR = 0.689, 95% CI (0.557–0.851), p < 0.001] and SHBG [OR = 0.903, 95% CI (0.849–0.960), p = 0.001] were independent inverse predictors (Table 3).

Diagnostic performance of free testosterone for prediction well coronary collateral flow: Receiver operating characteristic (ROC) curve analysis was conducted to establish the cut-off value for free testosterone using the Youden index and assess its diagnostic performance. The area under the curve (AUC) demonstrated that free testosterone is a strong diagnostic marker for predicting WCF. At the optimal cut-off of 9.31, free testosterone predicted WCF with 77% sensitivity and 86% specificity (AUC 0.81, 95% CI 0.744–0.880, $p<0.001$ (Figure 1).

Discussion

Our study demonstrates a significant association between high serum sex steroid levels and well CCC in male patients with coronary artery occlusion. This finding adds to the growing body of evidence emphasizing the critical role of androgens, particularly free testosterone, in cardiovascular health and disease progression.

The observed decrease in serum total testosterone and DHEA-S levels in patients with coronary occlusion and poor CCC is consistent with previous studies that identified low androgen levels as important predictors of CAD severity (21,22). Sensitivity analyses in our study highlighted free testosterone as the most important predictor of the

Table 1 : Demographic Features and Laboratory Tests of The Study Population

	Control Group (n=29) (A)	Group PCF (n=50) (B)	Group WCF (n=99) (C)	p value*	Pairwise Comparison A-B	B-C	A-C
Age, years; Mean±SD	57.2±3.81	57.1 ± 7.8	58.9 ± 6.4	0.040	0.162	0.983	0.061
Hip circumference, cm; Mean±SD	9.9±6.72	102.8 ± 8.8	102.7 ± 9.2	0.795	NS	NS	NS
Waist circumference, cm; Mean±SD	104±17.9	100.3 ± 11.8	101.7 ± 11.1	0.813	NS	NS	NS
BMI, kg/m²; Median [IQR]	28.5±2.48	28.7 ± 2.9	29.9 ± 4.1	0.078	NS	NS	NS
Total occlusion; n (%)							
LAD		17 (34)	40 (40.0)				
Cx		14 (28)	19 (19.1)	0.690			
RCA		25 (50)	34 (34.3)				
Diabetes mellitus; n (%)	5 (17.2)	28 (56)	23 (23.2)	<0.001	<0.001	0.043	<0.001
Hypertension;n (%)	6 (20.6)	17 (34)	26 (26.3)	0.428	NS	NS	NS
Smoking; n (%)	7 (24.1)	30 (60)	28 (28.3)	<0.001	<0.001	0.054	<0.001
Family history of CVD; n (%)	8 (13.79	19 (38)	26 (26.3)	0.199			
Creatinine, mg/dl; Median [IQR]	0.9 (0.8-1.1)	0.9 [0.8 - 1.0]	0.9 [0.8 - 1.0]	0.161	NS	NS	NS
Total cholesterol, mg/dl; Mean±SD	226.2±36.9	221.9 ± 41.1	219.0 ± 37.0	0.650	NS	NS	NS
LDL-cholesterol, mg/dl; Mean±SD	121.1±26.1	120.1 ± 34.6	118.3 ± 30.3	0.796	NS	NS	NS
HDL-cholesterol, mg/dl; Mean±SD	49.3±6.2	47.2 ± 7.4	48.1 ± 7.3	0.506	NS	NS	NS
Triglyceride, mg/dl; Median [IQR]	232.1[191.1-367.6]	240.0 [181.2 - 327.5]	220.0 [132.5 - 375.0]	0.425	NS	NS	NS
Hemoglobin, g/dl; Mean±SD	12.9±1.4	12.5 ± 1.2	13.1 ± 1.2	0.059	NS	NS	NS
Leukocyte count, *1000/dl; Mean±SD	7.6±1.5	7.8 ± 1.1	7.9 ± 0.8	0.925	NS	NS	NS
Platelet count, *1000/dl; Median [IQR]	300.0[175.1-355.0]	252.5 [190.5-288.0]	274.0 [193.0 - 364.5]	0.800	NS	NS	NS
LVEF; %; Mean±SD	60±5.0	59.5 ± 5.	58.3 ± 6.6	0.282	NS	NS	NS
Total testosterone, ng/dl; Mean±SD	382±56.8	273.8 ± 59.9	350.6 ± 78.5	<0.001	<0.001	0.038	<0.001
Free testosterone, pg/ml; Mean±SD	11.6±3.81	7.2 ± 2.0	12 .1 ± 3.3	<0.001	<0.001	0.861	<0.001
DHEAS, µg/dl; Mean±SD	205±72.4	131.9 ± 87.9	180.5 ± 69.5	<0.001	<0.001	0.228	0.003
SHBG, nmol/L; Mean±SD	34.5±9.2	24.8 ± 6.9	35.3 ± 11.0	<0.001	<0.001	0.849	<0.001

p<0.05 was considered statistical significant. Abbreviations: BMI, body mass index; Cx, circumflex artery; CVD, cardiovascular disease; DHEAS, dihydroxy-epiandrostenedione sulfat; IQR_{25-75}, interquartile range; LAD, left anterior descending artery; LVEF, left ventricular ejection fraction; NS, nonsignificant; RCA, right coronary artery; SD, standard deviation; SHBG, sex-hormone-binding globuline; PCF, poor collateral function; WCF, well collateral function

Table 2. Results of The Ordinal Logistic Regression Analyses Conducted to Identify Variables That May Predict the Presence of Coronary Collateral Flow

	OR	CI 95%	p value*
Age	0.991	0.942-1.043	0.737
Diabetes Mellitus	1.785	0.878-3.681	0.112
Smoking	1.933	0.981-3.868	0.059
Total testosterone	0.992	0.987-0.997	0.002
Free testosterone	0.870	0.794-0.951	0.002
DHEAS	0.996	0.991-1.000	0.054
SHBG	0.977	0.944-1.040	0.171

p<0.05 was considered statistical significant. Abbreviations CI; confidence interval; DHEAS, dihydroxy-epiandrostenedione sulfat; OR, odds ratio; SHBG sex-hormone-binding globuline

Table 3: Results of the Binominal Regression Analyses Performed For Identifying The Variables That May Anticipate The Presence of Poor Collateral Flow

	OR	CI 95%	p value*
Age	0.917	0.842-1.02	0,056
Diabetes Mellitus	1.923	1.041-4.092	0.012
Smoking	1.740	0.660-4.588	0.263
Total testosterone	0.997	0.990-1.004	0.401
Free testosterone	0.689	0.557-0.851	<0.001
DHEAS	0.998	0.991-1.004	0.500
SHBG	0.903	0.849-0.960	0.001

* p<0.05 was considered statistical significant. Abbreviations CI; confidence interval; DHEAS, dihydroxy-epiandrostenedione sulfat; OR, odds ratio; SHBG sex-hormone-binding globuline

development of CCC. This is consistent with established data showing that testosterone facilitates epicardial coronary artery dilation and increases volumetric blood flow, suggesting a protective vascular role (23,24). Potential mechanisms by which low androgen levels contribute to the development of poor CCC may involve several physiological pathways. Testosterone and other androgens are known to affect endothelial function, inflammatory responses, and vascular smooth muscle cell activity (23-25). There are also studies showing that androgens play a role in angiogenesis and atherogenesis at the microvascular level. In particular, it contributes by triggering transcriptional control target genes controlled by androgen receptors and by enhancing the interaction of multiple signalling pathways (8,9). Testosterone, the primary androgen, improves endothelial function by increasing nitric oxide production, which promotes vasodilation and boosts blood flow, thereby generating shear stress that stimulates the formation of collateral vessels (27). Additionally, testosterone upregulates angiogenic factors like vascular endothelial growth factor and fibroblast growth factor, facilitating the growth of new blood vessels (26,27). It also modulates inflammation, reducing chronic inflammatory markers while supporting acute inflammatory responses crucial for vascular repair (28). These effects collectively explain why men, with higher endogenous testosterone levels, often exhibit more robust collateral vessel formation, highlighting the potential of androgen-based therapies to improve outcomes in patients with CAD (29,30). Understanding these mechanisms paves the way for developing targeted treatments that leverage the cardiovascular benefits of androgens while minimizing potential risks.

Our findings also suggest that diabetes is an important risk factor for the development of poor CCC, which is confirmed by previous studies that have linked diabetes to impaired collateral vessel formation (31). However, in contrast to some studies, we did not find a significant association between HT, BMI and CCC. Additionally, we found no significant association between smoking and collateral development. This finding contrasts with other studies showing a significant association between smoking and collateral growth (32). However, variability in these findings may be due to differences in study populations and methodologies.

Our study adds to the clinical evidence that low

serum sex steroid levels are a marker of poor CCC in men with coronary occlusion. This highlights the importance of considering sex steroid levels in the management and prognosis of CAD.

Despite these important findings, our study has limitations. The relatively small sample size may limit the generalizability of our results, and the observational nature of the study cannot establish causality. Additionally, variability in hormone levels due to factors such as age, comorbidities, and lifestyle factors should be taken into account. Future larger and longer-term studies will confirm our findings and contribute to elucidating the mechanisms underlying the link between sex steroids and CCC.

In conclusion, our study highlights the importance of sex steroids in coronary collateral development. High free testosterone and SHBG levels are significant predictors of well CCC in male patients with coronary occlusion. These findings highlight the need for further research to better understand the complex interactions between sex steroids and cardiovascular health, potentially leading to improved treatment strategies for CAD patients.

Ethics Committee Approval: The study adhered to the ethical guidelines outlined in the Declaration of Helsinki and received approval from the local ethics committee in July 2024 (reference number 2024 - 07-1147).

Informed Consent: Due to the retrospective nature of the study, the requirement for written informed consent from participants was waived.

Acknowledgements: We sincerely thank Ass. Prof. Dr. Omer Genc for his invaluable assistance and expertise in conducting the statistical analysis for this project. His guidance and insights significantly enhanced the rigour and quality of our work.

Conflict of Interest: The authors declare no conflicts of interest.

Financial Disclosure: The authors confirm that no financial support was received for this study.

References

1. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Christian Funck-Brentano, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes: The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). Europ Heart J 2019; 41: 407- 77.
2. Visseren FL, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice: Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies with the special contribution of the European Association of Preventive Cardiology (EAPC). Europ Heart J 2021; 42(34):3227-3337.
3. Schwarz F, Flameng W, Ensslen R, Sesto M, Thormann J. Effect of collaterals on left ventricular function at rest and du-ring stress. Am Heart J 1978; 95: 570-577.
4. 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.
5. Wolfgang S, Scholz D.Factors regulating arteriogenesis. Arteriosclerosis Thromb Vasc Bio 2003; 23(7): 1143-1151.
6. Altman JD, Bache RJ. The coronary collateral circulation. ACC Current J Review 1997; 6(1): 17-21.
7. Conway EM, Collen D, Carmeliet P. Molecular mechanisms of blood vessel growth. Cardiovasc Res 2001; 49: 507-21.
8. 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.
9. 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.
10. Haring R, Völzke H, Steveling A, Krebs A, Felix SB, Schöfl C, et al. Low serum testosterone levels are associated with an increased risk of mortality in a population-based cohort of men aged 20-79. Eur Heart J 2010; 31: 1494-501.
11. 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.
12. Yeap BB, Alfonso H, Chubb SA, Handelsman DJ, Hankey GJ, Almeida OP et al. In older men, 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.
13. Corona G, Rastrelli G, Di Pasquale G, Sforza A, Mannucci E, Maggi M. Endogenous testosterone levels and cardiovascular risk: a metaanalysis of observational studies. J Sex Med 2018; 15: 1260–71.
14. 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.
15. Yeap BB, Marriott RJ, Antonio L, Raj S, Dwivedi G, Reid CM. Associations of serum testosterone and sex hormone–binding globulin with ıncident

cardiovascular events in middle-aged to older men. Ann Intern Med 2022; 175(2): 159-170.

16. Kalme T, Seppälä M, Qiao Q, Koistinen R, Nissinen A, Harrela M, et al. Sex hormone-binding globulin and insulin-like growth factor-binding protein-1 as indicators of metabolic syndrome, cardiovascular risk, and mortality in elderly men. The J Clinical Endocrinol Metab 2005;90(3): 1550-1556.
17. Hunsicker LG, Adler S, Caggiula A, England BK, Gerene T, Kusek JW, et al. Predictors of the progression of renal disease in the Modification of Diet in Renal Disease Study. Kidney Int 1997; 51(6): 1908-1919.
18. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo Jr JL, et al. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. Hypertension 2003; 42(6): 1206-1252.
19. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on the detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA 2001; 285(19): 2486-2497.
20. 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.
21. Tang L, Chen M, Li J, Xu X, Pu X. Association of testosterone with myocardial infarction and severity of coronary artery disease among male patients. Int J Cardiol Cardiovasc Risk and Prev 2024; 21: 200281.
22. Tivesten Å, Vandenput L, Carlzon D, Nilsson M, Karlsson MK, Ljunggren Ö, et al. Dehydroepiandrosterone and its sulfate predict the 5-year risk of coronary heart disease events in elderly men. J Am Coll Cardiol 2014; 64(17): 1801-1810.
23. 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.
24. Babcock MC, DuBose LE, Witten TL, Stauffer BL, Hildreth KL, Schwartz RS,et al. Oxidative stress and inflammation are associated with age-related endothelial dysfunction in men with low testosterone. The J Clinical Endocrinol Metab 2022;107(2): 500- 514.
25. 25. Fu L, Gao QP, Shen JX. Relationship between testosterone and indexes indicating endothelial function in male coronary heart disease patients. Asian J Androl 2008; 10: 214–8.
26. 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.
27. Mancini A, Leone E, Festa R, Grande G, Silvestrini A, De Marinis L, et al. Effects of testosterone on antioxidant systems in male secondary hypogonadism. J Androl 2008; 29(6): 622-629.
28. Mohamad NV, Wong SK, Hasan WN, Jolly JJ, Nur-Farhana MF, Ima-Nirwana S, et al. The relationship between circulating testosterone and inflammatory cytokines in men. Aging Male 2019;22(2):129-140.
29. 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.
30. 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.
31. Pei J, Wang X, Xing Z. Traditional cardiovascular risk factors and coronary collateral circulation: a meta-analysis. Front
32. Cardiovasc Med 2021; 8(3): 743234.
33. Koerselman J, Peter PT, Verhaar MC, Grobbee DE, van der Graaf Y, and SMART Study Group. Coronary collateral circulation: the effects of smoking and alcohol. Atherosclerosis 2007; 191(1):191-198.