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Impact of Serum Testosterone Titres on Complexity of Coronary Lesions in Premature Ischemic Egyptian Males: Angiographic Based Study

Remon Saleh Adly *[1], Sherein Feleeb Aziz [2]
Department of [1]Cardiology and [2]Clinical Pathology, Faculty of Medicine, Sohag University, Sohag, Egypt
*** Corresponding author:** Remon Saleh Adly, **Email:** remonsaleh@yahoo.com,
Mobile: +201221878986, **ORCID:** 0009-0003-1666-7299

ABSTRACT

Background: Premature ischemic heart disease (IHD) is a significant health concern, particularly in young males, who are often not considered at high risk for coronary artery disease (CAD).

Objective: This work investigated the association between serum testosterone titres and the angiographic complexity of coronary lesions in males <45 years presenting with premature IHD.

Patients and Methods: This prospective study involved 50 male patients, <45 years, diagnosed with premature IHD, and undergoing elective coronary angiography. Patients were divided based on the complexity of coronary lesions (by SYNTAX score) into two equal groups: the significant CAD and the Non-complex CAD groups. Before coronary angiography, hormonal assays for testosterone titres and routine laboratory investigations were done.

Results: Total testosterone and SHBG were comparable between the groups. The significant CAD group had substantially diminished free testosterone as opposed to the non-complex CAD group [0.09 (0.04-0.21) vs 0.19 (0.09-0.35) ng/dl, P=0.01]. Luteinizing (LH) and follicle-stimulating (FSH) hormones, and estradiol were substantially elevated in the significant CAD group (P<0.001). Multivariate regression confirmed that serum albumin, total testosterone, free testosterone, FSH, and estradiol were independent predictors of coronary lesion complexity (P<0.05).

Conclusions: In premature ischemic Egyptian males, diminished serum testosterone titres were substantially associated with increased complexity of coronary artery lesions. Free testosterone emerged as an independent predictor of lesion complexity.

Keywords: Premature Ischemic Heart Disease, Testosterone, SYNTAX Score, Coronary Artery Disease, Lesion Complexity

INTRODUCTION

Coronary artery disease (CAD) continues to be a significant etiology of global mortality and morbidity. Although traditionally linked with older age groups, there is a noticeable increase in the occurrence of premature CAD [1]. This younger cohort often does not exhibit typical risk factors like diabetes or hypertension, which has spurred research into alternative causes for early-onset atherosclerosis. Recent studies suggest that hormonal imbalances, particularly low serum testosterone, could substantially contribute to the development of premature CAD [2].

Testosterone, the dominant male sex hormone, affects several physiological functions aside from its role in reproduction. It impacts muscle mass, fat distribution, insulin sensitivity, and vascular tone. Reduced testosterone titres are associated with poor metabolic outcomes, including elevated adiposity, dyslipidemia, and insulin resistance, all well-known risk factors for atherosclerosis. Testosterone deficiency has been linked to endothelial dysfunction, an early event in atherosclerotic plaque development [3].

Numerous studies have revealed a negative correlation between serum testosterone titres and CAD severity. Men with diminished testosterone titres tend to show more severe coronary lesions and elevated angiographic scores, suggesting a more complex disease process. This relationship remains even when traditional cardiovascular risk factors are taken into account, implying that testosterone plays an independent role in regulating coronary atherosclerosis [4,5].

The ways in which testosterone influences CAD are complex. Testosterone promotes vasodilation by increasing nitric oxide production, reduces inflammatory cytokine titres, and inhibits the proliferation of vascular smooth muscle cells. These combined effects help maintain vascular health and prevent atherogenesis. On the other hand, testosterone deficiency may heighten inflammatory responses and endothelial dysfunction, potentially accelerating plaque development and progression [6].

The angiographic evaluation of coronary lesions offers significant insights into the severity and complexity of atherosclerotic disease [7]. The SYNTAX score, a commonly used assessment tool, measures lesion complexity based on factors such as location, length, and morphology. Elevated SYNTAX scores are linked to poorer clinical outcomes and influence revascularization strategies [8]. Exploring the connection between serum testosterone titres and SYNTAX scores in young males could improve risk assessment and help guide therapeutic interventions [4].

Despite growing evidence of the relationship between low testosterone and increased severity of CAD, there is limited data on this connection in younger males. Most studies have focused on middle-aged or older populations, leaving a knowledge gap regarding testosterone's influence on coronary lesion complexity in men under 45 years of age [9,10].

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Addressing this gap is crucial, as early identification of high-risk individuals could facilitate timely interventions and improve long-term outcomes. Hence, this work investigated the association between serum testosterone and the angiographic complexity of coronary lesions in males under 45 years presenting with premature IHD.

PATIENTS AND METHODS

This prospective cohort study enrolled 50 male patients under the age of 45 years who were diagnosed with premature IHD and scheduled for elective coronary angiography. Based on the angiographic complexity of their coronary lesions, as quantified by the SYNTAX score, patients were evenly divided into two groups: those with significant CAD and those with non-complex CAD.

Participants with a recent history (within the past three months) of acute coronary syndrome, previously diagnosed hypogonadism, ongoing or prior testosterone therapy or anabolic steroid use were excluded. Additional exclusion criteria encompassed known malignancies or prior chemotherapy, hepatic cirrhosis, chronic or end-stage renal disease, current use of medications known to interfere with sex hormone levels (e.g., ketoconazole or spironolactone), and endocrine conditions such as celiac disease or sickle cell anemia.

All participants underwent comprehensive clinical assessment, including thorough personal and family medical histories. Particular attention was paid to the documentation of traditional cardiovascular risk factors such as diabetes mellitus, hypertension, dyslipidemia, active smoking, and familial predisposition to early CAD—defined as cardiovascular events occurring before age 55 in male relatives and before age 65 in female relatives. Baseline investigations included complete blood count, fasting blood glucose, renal and ;hepatic function panels, and lipid profile. In addition, all patients received a standard 12-lead electrocardiogram and transthoracic echocardiography to complete their initial cardiovascular evaluation.

At a rate of 12.5 frames per second, digital angiographic pictures were captured using an angiography Philips Integris 2000 (Philips: Harvey IL 60426, USA).

CAD was defined as having more than 70% stenosis in at least one major epicardial artery or more than 50% stenosis in left main coronary artery (LMCA).

Blood Sample Collection and Hormonal Analysis

Prior to undergoing coronary angiography, each participant provided a 10 mL venous blood sample following an overnight fast. The collected samples were centrifuged at 3500 revolutions per minute for 9 minutes, after which the separated serum was preserved at −80°C until hormonal analysis. The assays included measurements of total and free testosterone, sex hormone-binding globulin (SHBG), luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, and serum albumin concentrations. All hormone levels were quantified using validated commercial assay kits, and testosterone titres were specifically assessed via chemiluminescence-based detection methods. According to the assay's reference standards, serum testosterone values below 9 ng/dL were considered subnormal for adult males.

Coronary Angiography and SYNTAX Scoring:

The complexity of coronary artery disease was evaluated angiographically using the SYNTAX scoring system, which integrates multiple lesion-specific parameters. These include the total number of lesions, coronary dominance, anatomical location, morphological characteristics, percentage stenosis, and the presence of complicating features such as total occlusion, bifurcation or trifurcation involvement, heavy calcification, severe vessel tortuosity, intraluminal thrombus, and diffuse disease affecting small-caliber vessels. Based on total SYNTAX scores, patients were stratified into three risk categories: low (≤22), intermediate (23–32), and high (≥33). According to these stratifications, individuals were further classified into either the significant CAD group or the non-complex CAD group depending on the cumulative lesion burden and anatomical complexity.

Sample size calculation

The sample size for this study was estimated using G*Power 3.1.9.2 (Universität Kiel, Germany), aiming for a significance level of 0.05 and 95% power to detect a 20% increase in serum testosterone levels in the non-CAD group as opposed to the CAD group (mean 3.91, SD 0.65, based on previous research [3]). To mitigate the potential impact of participant dropouts, 10 additional cases were included, resulting in a total of 50 patients.

Ethical Considerations

The study was approved by the Research Ethics Committee of the Faculty of Medicine, Sohag University. Written informed consent was obtained from all participants prior to enrollment. The consent process ensured that participants fully understood the nature and purpose of the study, as well as their rights, including the confidentiality of their personal information and the use of anonymized data for publication. This research was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and adhered to all relevant institutional and national guidelines for studies involving human participants.

Statistical analysis

All statistical computations were conducted using IBM SPSS Statistics software, version 29 (IBM Corp., Armonk, NY, USA). The normality of data

distribution was evaluated through the Shapiro–Wilk test and by visual inspection of histograms. Variables exhibiting normal distribution were described using mean values and standard deviation (SD), and intergroup comparisons were made using the independent samples t-test. For non-normally distributed data, results were expressed as medians with interquartile range (IQR), and comparisons between groups were carried out using the Mann–Whitney U test. Categorical variables were summarized as frequencies and percentages and were analyzed using either the Chi-square test or Fisher's exact test, depending on expected cell counts. To explore associations between clinical or laboratory parameters and coronary lesion complexity, univariate logistic regression was initially performed. Variables with significant associations in univariate analysis were subsequently included in a multivariate logistic regression model to identify independent predictors. All statistical tests were two-sided, and a p-value ≤ 0.05 was regarded as indicative of statistical significance.

RESULTS

There were no statistically significant variations between the two groups in terms of age, body weight, presence of diabetes mellitus or hypertension, smoking status, or family history of CAD. However, dyslipidemia was substantially more frequent among patients in the significant CAD group compared to those in the non-complex group ($P < 0.001$) (Table 1).

Table 1: Demographic data and risk factors of the studied groups

	Significant CAD group (n=25)	Non-complex CAD group (n=25)	P	MD, odds ratio (95%CI)
Age (years)	35.24 ± 4.86	32.8 ± 6.24	0.130	2.44 (-0.74: 5.62)
Weight (kg)	81.64 ± 6.06	83.4 ± 6.98	0.346	-1.76 (-5.48 :1.96)
CAD family history	18 (72%)	13 (52%)	0.145	2.37 (0.73: 7.68)
Diabetes mellitus	18 (72%)	21 (84%)	0.496	0.49 (0.12: 1.95)
Hypertension	21 (84%)	19 (76%)	0.725	1.66 (0.41: 6.79)
Dyslipidemia	19 (76%)	4 (16%)	**<0.001***	16.63 (4.06: 68.04)
Smoking	6 (24%)	5 (20%)	0.733	1.26 (0.33: 4.84)

Data are presented as mean ± SD or frequency (%). CAD: Coronary artery disease. MD: Mean variation, CI: Confidence interval, *: Significant as P<0.05.

Hemoglobin, WBCs, platelets, fasting blood glucose, urea, creatinine, ALT, and AST were comparable between the groups. However, LDL, triglycerides, and albumin titres were substantially elevated in the significant CAD group as opposed to the non-complex CAD one (P<0.05). HDL titres were substantially diminished in the significant CAD group in contrast with the non-complex CAD one (P<0.001) (Table 2).

Table 2: Laboratory tests of the studied groups

	Significant CAD group (n=25)	Non-complex CAD group (n=25)	P	MD (95%CI)
Hemoglobin (g/dL)	12.74 ± 1.1	13.36 ± 1.48	0.098	-0.62(-1.37 :0.12)
WBCs (10^3/µL)	9.25 ± 2.89	8.1 ± 2.52	0.141	1.15(-0.39: 2.69)
Platelets (10^3/µL)	241.36 ± 47.11	257.88 ± 5.6	0.263	-16.52(-45.82: 12.78)
Fasting blood glucose (mg/dL)	150.44 ± 5.89	161.84 ± 40.47	0.356	-11.4(-36.01 :13.21)
LDL (mg/dL)	117.28 ± 23.53	88.76 ± 15.68	**<0.001***	28.52(17.15: 39.89)
HDL (mg/dL)	33.28 ± 4.63	55.44 ± 18.63	**<0.001***	-22.16(-31.69: -12.63)
Triglycerides (mg/dL)	159.6 ± 18.82	131.8 ± 16	**<0.001***	27.8(17.87: 37.73)
Creatinine (mg/dL)	1.18 ± 0.2	1.15 ± 0.24	0.687	0.04(-0.15: 0.23)
Urea (mg/dL)	18.16 ± 4.34	17.2 ± 3.55	0.458	0.96(-1.62: 3.54)
ALT (U/L)	40.36 ± 9.5	38.8 ± 5.29	0.754	1.56(-8.4: 11.52)
AST (U/L)	33.52 ± 8.98	32.44 ± 1.79	0.702	1.08(-4.57: 6.73)
Serum albumin (gm/dl)	4.72 ± 0.37	4.38 ± 0.49	**0.01***	0.33(0.08: 0.58)

Data are presented as mean ± SD. WBCs: White blood cells, LDL: Low density lipoprotein, HDL: High density lipoprotein, ALT: Alanine transaminase, AST: Aspartate transferase, CAD: Coronary artery disease. MD: Mean variation, CI: Confidence interval, *: Significant as P<0.05.

Total testosterone and SHBG titres were similar between both groups. The median (IQR) free testosterone was 0.09 (0.04 - 0.21) ng/dl in the significant CAD group, and 0.19 (0.09 - 0.35) ng/dl in the non-complex CAD one, with the significant CAD group showing substantially diminished titres (P=0.01). LH, FSH, and estradiol titres were substantially elevated in the significant CAD group as opposed to the non-complex one (P<0.001) (Table 3).

Table 3: Hormonal data of the studied groups

	Significant CAD group (n=25)	Non-complex CAD group (n=25)	P	MD, median variation (95%CI)
Total testosterone (ng/dl)	3.59(2.12 - 4.36)	4.75(1.99 - 7.31)	0.067	1.65(-0.09: -3.14)
Free testosterone (ng/dl)	0.09(0.04 - 0.21)	0.19(0.09 - 0.35)	**0.01***	0.08(0.02: 0.20)
SHBG (nmol/L)	44.68 ± 4.4	47.56 ± 7.25	0.525	-2.88(-11.92 :6.16)
LH (ng/dl)	6.17(3.94 - 9.85)	3.48(2.84 - 4.46)	**<0.001***	-3.06(-5.39: -1.23)
FSH (ng/dl)	8.92 ± 2.7	4.96 ± 1.79	**<0.001***	3.96(2.31: 5.61)
Estradiol (pg/mL)	39.76 ± 7.86	25.12 ± 1.18	**<0.001***	14.64(9.47: 19.81)

Data are presented as mean ± SD. SHBG: Sex hormone-binding globulin, LH: Luteinizing hormone, FSH: Follicle-stimulating hormone, CAD: Coronary artery disease. MD: Mean variation, CI: Confidence interval, *: Significant as P<0.05.

In univariate regression, dyslipidemia, LDL, HDL, triglycerides, serum albumin, total and free testosterone, LH, FSH, and estradiol titres were independent predictors of coronary artery lesion complexity (P<0.05). In multivariate regression, serum albumin, total testosterone, free testosterone, FSH, and estradiol titres remained independent predictors of lesion complexity (P<0.05) (Table 4 and Figure 1).

Table 4: Univariate and multivariate regression of different variables versus complexity of coronary artery lesions

	Univariate			Multivariate		
	OR	**95% CI**	**P**	**OR**	**95% CI**	**P**
Age	1.08	0.977-1.2	0.130	---	---	---
Dyslipidemia	16.63	4.05-68.04	**<0.001***	0.002	0-39.36	0.210
LDL (mg/dL)	1.06	1.02-1.09	**<0.001***	1.05	0.936-1.18	0.399
HDL (mg/dL)	0.932	0.897-0.969	**<0.001***	0.967	0.883-1.06	0.469
Triglycerides (mg/dL)	1.073	1.036-1.11	**<0.001***	1.16	0.948-1.41	0.151
Serum albumin (gm/dl)	5.73	1.39-23.51	**0.015***	9.51	1.08-83.7	**0.042***
Total testosterone (ng/dl)	0.713	0.536-0.947	**0.019***	0.588	0.398-0.866	**0.007***
Free testosterone (ng/dl)	0.002	0-0.26	**0.013***	0.0002	0-0.079	**0.005***
SHBG (nmol/L)	0.988	0.954-1.024	0.516	---	---	---
LH (ng/dl)	1.945	1.24-3.06	**0.004***	1.365	0.862-2.16	0.185
FSH (ng/dl)	1.674	1.23-2.27	**0.001***	1.589	1.03-2.46	**0.037***
Estradiol (pg/mL)	1.20	1.086-1.33	**<0.001***	1.251	1.04-1.49	**0.015***

CI: Confidence interval, OR: Odds ratio. LDL: Low density lipoprotein, HDL: High density lipoprotein, SHBG: Sex hormone-binding globulin, LH: Luteinizing hormone, FSH: Follicle-stimulating hormone, *: Significant as P<0.05.

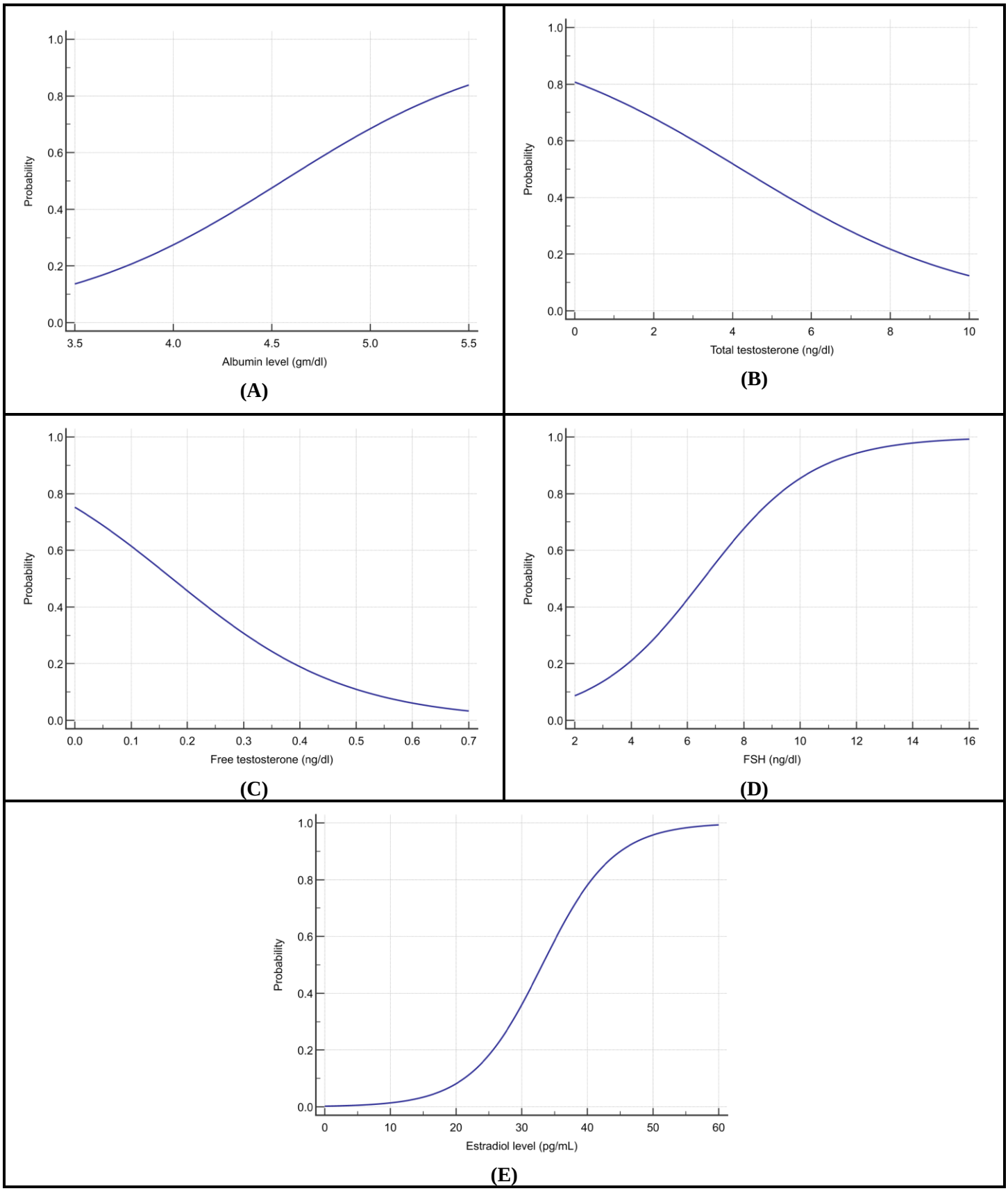

Figure 1: Regression analysis of (A) serum albumin, (B) total testosterone, (C) free testosterone, (D) FSH and (E) estradiol versus complexity of coronary artery lesions.

DISCUSSION

The novelty of our research lies in the inclusion of patients under 45 years of age (unlike the typical 55-year cut-off in the literature) along with intergroup comparisons between significant and non-significant CAD, and a comprehensive assessment of lesion complexity in relation to total and free testosterone, SHBG, LH, FSH, and estradiol levels.

The results of our investigation indicated that LDL, triglycerides, and albumin titres were substantially elevated in the significant CAD group, while HDL titres were substantially diminished. Additionally, the significant CAD group had diminished free testosterone titres and elevated titres of LH, FSH, and estradiol in contrast with the non-significant CAD group. Univariate regression identified several factors, including lipid titres, serum albumin, testosterone, and estradiol, as independent predictors of coronary artery lesion complexity, with multivariate regression confirming that serum albumin, testosterone, and estradiol remained significant predictors, while lipid titres and LH did not.

In addition to its role in vascular health, testosterone also exerts anti-inflammatory effects [11]. Diminished testosterone titres have been linked to elevated titres of inflammatory markers [12]. Chronic inflammation is a well-established factor in the pathogenesis of atherosclerosis and the development of complex coronary lesions. Testosterone deficiency may increase inflammation, leading to plaque instability and more severe coronary lesions [13].

Moreover, testosterone influences lipid metabolism by increasing HDL and decreasing LDL cholesterol. Dyslipidemia, characterized by elevated titres of LDL and triglycerides and diminished HDL, is a significant risk factor for atherosclerosis [14].

Testosterone is also crucial for insulin sensitivity. Diminished testosterone titres have been linked to insulin resistance, a key contributor to the development of cardiovascular diseases. Insulin resistance leads to elevated blood sugar titres, contributing to endothelial dysfunction and the progression of atherosclerosis [15].

SHBG, which binds to testosterone and regulates its bioavailability, may also play a role in this relationship [16]. Elevated SHBG titres can diminish the availability of free testosterone, and though SHBG titres were similar between the groups in this study, its indirect effect on testosterone bioavailability could still contribute to the observed variations in testosterone titres between the complex and non-significant CAD groups.

SHBG has been shown to correlate with cardiovascular risk factors, including atherosclerosis, suggesting that it might influence the testosterone-CAD association by modulating the effects of free testosterone [16].

In line with our results, **Badran and colleagues** [17] explored the link between testosterone titres and CAD severity in young males undergoing coronary angiography. Their analysis of 61 publications uncovered that both total and free testosterone levels were notably reduced in young males with CAD, with a strong correlation between these levels and the severity of CAD, as measured by the Gensini score. The findings suggest that low testosterone is linked not only to the onset but also to the progression of early-onset CAD in young males. However, they did not investigate the titres of LH or FSH, they also depended on the Gensini score not the SYNTAX one, which is broader and more accurate.

In the same context, **Sezavar and co-authors** [18] assessed the presence of CAD with testosterone titres. They exhibited that diminished testosterone titres were associated with the presence of CAD, though they did not observe a correlation between testosterone titres and lesion complexity, unlike our results. They reported no statistically significant correlation between the free or total testosterone levels and the SYNTAX score in CAD males younger than 55 years. This variation may be due to the variation in the included age.

From a different view, **Erdoğan and colleagues** [19] exhibited that patients with poor coronary collateral flow (PCF) had substantially diminished titres of total and free testosterone, dehydroepiandrosterone sulfate, and SHBG in contrast with both control subjects and patients with well coronary collateral flow. Also, free testosterone and total testosterone were identified as independent predictors of coronary collateral flow. Free testosterone titres were inversely associated with poor coronary collateral flow.

Although **Chiang and co-authors** [20] identified a connection between low serum testosterone levels and an increased risk of major adverse cardiovascular events as well as the requirement for target lesion or vessel revascularization following percutaneous coronary intervention, however, their investigation exhibited no significant association between low testosterone titres and the severity of CAD, as evaluated by the SYNTAX score in our study.

In contrast with our analysis , a cross-sectional analysis of 40 men aged more than 40 years with CAD by **Badrinath and collaborators** [21], reported that although patients exhibited reduced free testosterone levels, these levels did not show a significant correlation with disease severity based on the number of affected vessels or the complexity of the lesions. This might be attributed to different range of included age and under estimation of other hormonal titres.

Despite smoking and diabetes as common risk factors for CAD did not differ substantially between the significant and non-significant groups in our study, they remained common among participants, particularly diabetes, which was present in over 70% of both groups.

This reflects their established role in vascular pathology, as also highlighted by **Ikhdour and colleagues** [22] who determined that smoking and diabetes are significant risk factors in the progression and outcomes of acute ischemic stroke in the West Bank of Palestine and noted that these factors as major contributors to worse outcomes in stroke patients.

One limitation of the study is its limited sample size, which may not provide a comprehensive representation of the wider population of young men with premature IHD. The study also only included male patients under 45 years, limiting the generalizability of the observations to other populations. Moreover, the reliance on the SYNTAX score, although widely and strongly used, may not capture all aspects of CAD, particularly in diffuse small vessel disease, which was not thoroughly assessed in this study. It is recommended that future research further explore the role of serum testosterone, particularly free testosterone, in predicting the angiographic complexity of coronary lesions. Additional investigations with larger sample sizes and long-term follow-up are required to confirm these findings.

CONCLUSION

In premature ischemic Egyptian males, diminished serum testosterone titres were substantially associated with increased complexity of coronary artery lesions. While total testosterone and SHBG titres were comparable between the groups, free testosterone emerged as an independent predictor of lesion complexity.

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