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INCREASED INSULIN RESISTANCE, DYSLIPIDEMIA, PRO-INFLAMMATORY MARKERS AND ENDOTHELIAL DYSFUNCTION IN CASTRATED MALE RATS: ROLE OF TESTOSTERONE REPLACEMENT

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ABSTRACT: Molecular effects of androgens on cardiovascular system are variable in nature and are concentration dependent. In spite of the evidences favoring possible involvement of reduced endogenous androgens in the pathogenesis of atherosclerotic vascular disease, there is no certain role of exogenous testosterone supplementation in normal or hypogonadal males to slow down the progression of atherosclerosis. Replacement of testosterone in certain trials resulted in significant reduction in the levels of inflammatory mediators which are considered as important biomarkers in atherosclerosis. Present study aimed mainly to configure firstly the onset of inflammatory markers, dyslipidemia, insulin resistance, endothelial dysfunction (cardiovascular risk factors) as developed in castrated male rats. Secondly the role of testosterone replacement using various dose levels, expressed as low, medium and high respectively. Certain Biomarkers were selected for evaluation and are mainly serum glucose, insulin, lipogram pattern, CRP, IL-6, Endothelin-1 and plasma fibrinogen. Castration of rats and almost testosterone depletion has led to disturbance in glucose metabolism, lipogram pattern, increased inflammatory markers and plasma fibrinogen. Testosterone administration induced evident improvement, specifically more prominent on using medium dose.

INTRODUCTION: Androgens have been shown to be important for survival and many studies have concluded that endogenous testosterone levels are inversely related to mortality due to cardiovascular disease (CVD) as well as all causes. Therefore, low testosterone could be a predictive marker for those men at high risk of CVD and the relation between hypogonadism (chronic androgen insufficiency) and increased CVD has been suggested before [1].

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Hypogonadism may contribute to development of metabolic syndrome (Mets) which increases CVD risk [2] and Mets individuals demonstrates higher glucose, triglycerides (TGs), C-reactive protein (CRP), fibrinogen levels along with decreased high density lipoprotein cholesterol (HDL-C) level compared with controls and all of which were related to increased risk of CVD [3].

Therefore, testosterone has both a direct physiological role in maintaining CV health, independent of common risk factors [4], additionally an indirect role by modulating cardiac risk factors such as those implicated in the Mets. Men undergoing androgen deprivation therapy for prostate cancer develop hyperglycemia, insulin resistance and vascular disease [5]. Relationship

between androgen deficiency and lipid profiles was reported before. Many authors have suggested that reduced testosterone levels are associated with increased total cholesterol (TC) and low density lipoprotein cholesterol (LDL-c) [6]. Long-term anti androgenic treatment on the other hand as reported by certain study recorded also unique lipid profile, showing elevated TGs and decreased HDL-C values [7]. This suggests that anti-androgenic therapy contributes to CVD through changes in apoproteins (Apo A-I, Apo A-II), TG and HDL-C reduction.

Clinical and preclinical evidence linking endothelial dysfunction to androgen deficiency exist [8]. The relationship between androgen deficiency, endothelial dysfunction and vascular disease is very complex. Insulin resistance which is exacerbated by androgen deficiency might mediate endothelial dysfunction and vascular disease [9]. Clinical consequences of insulin resistance include dyslipidemia, hyperglycemia, hypertension, vascular inflammation and thrombotic risk inflammation [10-12].

Fibrinogen, acute phase protein is increased in inflammatory disease and have an inverse relationship with androgens and in particular testosterone, however it is not known how testosterone reduces fibrinogen [13]. Similar inverse relationship was also proved between endogenous testosterone and fasting glucose or insulin [14, 15]. Cumulative evidences originate from animal models indicated that castrated male animals rapidly develop atheroma which is abrogated by testosterone replacement [16] in a mechanism mostly attributed to inflammation development where testosterone can reduce inflammation additionally inflammatory cytokine [17, 18].

Present study therefore aimed mainly to configure firstly the changes in selected cardiovascular risk factors in consequence to castration initiated in male rats. Secondly to illustrate the effect of testosterone replacement therapy (TRT) using gradual doses, expressed as low, medium and high.

MATERIALS AND METHODS:

Animals:

Fifty male wistar rats weighing 170 ± 20 g were used in this study. Animal care was supervised and approved by the local ethical committee. Animals had free access to rat chow and water throughout the study.

Experimental design:

Castration was done after anesthetization of rats with sodium pentobarbital (60 mg/kg body weight I.P). Briefly, a small incision was made in the posterior tip of each scrotum sac, then the spermatic cord was tied with 4.0 silk sutures, and the testes were removed. The incision was closed with silk suture. The animals were given i.p injection of 50.000u/kg body weight Penicillin G benzathine and penicillin G procaine in aqueous suspension every 12 hours for 3 days to avoid any infection. The animals were allowed to recover and left for 8 weeks to guarantee serum testosterone depletion.

Castrated rats were randomly subdivided into 4 groups (n=10 rats each). The first group received no drugs, given IM sesame oil, expressed as castrated control (CC), while the other 3 groups received IM Testosterone Enanthate (Cidoteston, CID Co., EGYPT) dissolved in sesame oil at a ratio 1:2 (V/V) using a dose level of 8, 16 and 24 mg/kg body weight respectively once a week for 8 weeks.

Rats in sham group (n=10) received the same procedures as castrated rats without tying spermsatic cord or removing testes.

Blood sampling:

At the end of the experiment, rats were fasted overnight, blood samples were collected via retro-orbital bleeding and divided into two portions, the first one mixed with sodium citrate as anticoagulant and processed for fibrinogen determination while the other portion was processed for serum preparation. Serum glucose was instantly determined, subsequently the remaining sample was stored at (-20 ℃) as aliquots for further determination of CRP, interleukin-6 (IL-6), insulin, endothelin-1, free testosterone and lipid profile.

Biochemical investigations:

Serum level of glucose was determined using commercially available kit provided by spinreact, Spain according to the method of Trinder [19]. Serum

insulin level was measured using EIA kit provided by SPI bio Co, France. Insulin resistance was calculated from fasting serum glucose and insulin using the following formula: HOMA-IR= (glucose x insulin)/405 (Matthews et al., 1985). Serum CRP was measured using ELISA provided by BD Biosciences, USA according to the method of Banerjee et al [20]. IL-6 was determined using Ray Biotech ELISA kit, USA. Free testosterone was determined using Bio Line kit, Belgium. Total cholesterol (TC), HDL-cholesterol (HDL-C) and triglycerides (TAG) using Spinreact kits, Spain. Plasma fibrinogen was determined using commercial kits provided by Biomed, Cairo, Egypt. Endothelin-1 was determined by EIA assay design kit, USA following manufacturer's instructions.

Statistical analyses:

The statistical analyses were performed using Prism 5, Graph pad, CA, USA. The one way ANOVA test was used to evaluate the significance of the differences in parameters studied between groups. When the effect of groups was significant the differences were determined by means of the LSD Post Hoc test. All data are presented as mean ± SEM. Correlations were also determined using the Pearson correlation analysis. Differences were considered statistically significant at $p < 0.05$.

RESULTS:

Testosterone concentration:

Following castration, the serum testosterone levels dropped significantly reaching a very low plateau starting from week 4 following castration throughout study duration at week 8 (**Fig. 1A**). Testosterone enanthate replacement, once weekly, for 8 weeks raised the levels in a dose-dependent manner (**Fig. 1B**).

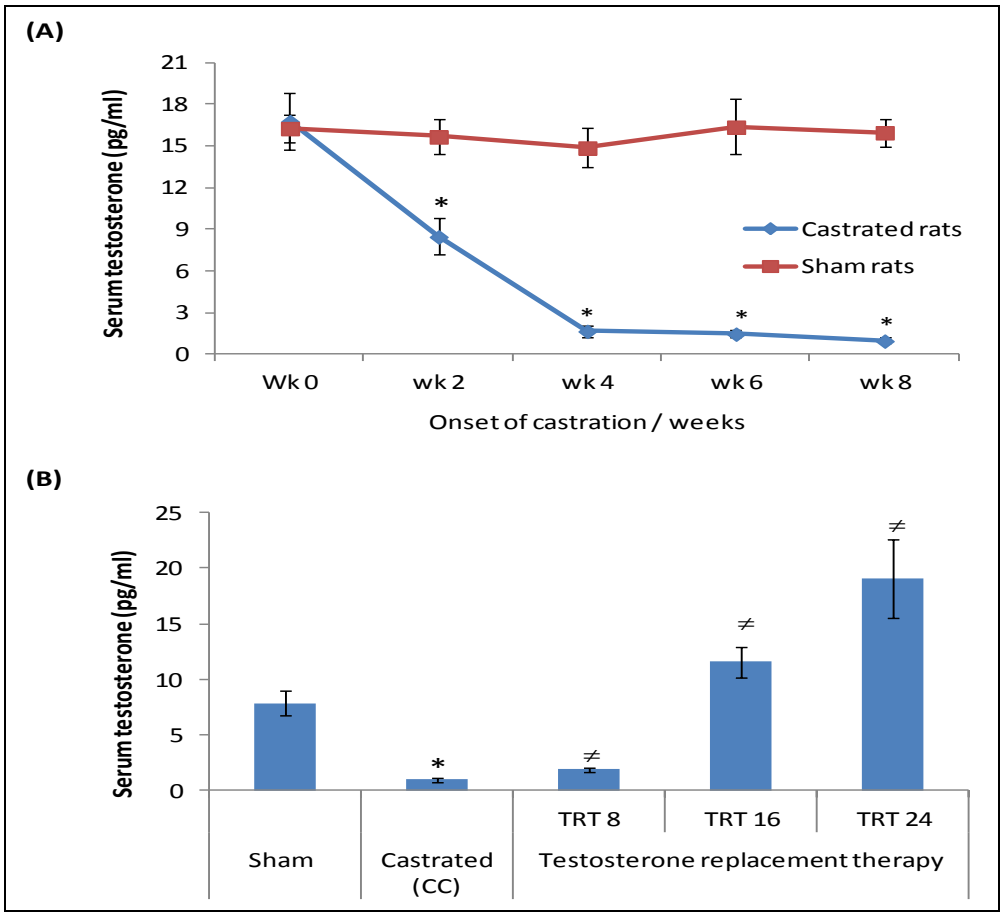

FIG.1: SERUM TESTOSTERONE (PG/ML) IN [A] CASTRATED MALE RATS VERSUS SHAM RATS AT 0, 2, 4, 6 AND 8 WEEKS AFTER CASTRATION AND [B] SHAM AND CASTRATED RATS (8 WEEKS AFTER CASTRATION) WITH AND WITHOUT TESTOSTERONE REPLACEMENT THERAPY. SHAM: SHAM OPERATED NON CASTRATED RATS, CC: CASTRATED CONTROL RATS (8 WEEKS AFTER CASTRATION), CASTRATED RATS (8 WEEKS AFTER CASTRATION) TREATED WITH TESTOSTERONE ENANTHATE 8 MG/KG (TRT 8) OR 16 MG/KG (TRT 16) OR 24 MG/KG (TRT 24).

Results were expressed as (Mean ± SEM), n= 6/group. *$p < 0.05$ CC vs. sham; $^{\neq}p < 0.01$, Treated Rats Vs. CC.

Fasting insulin sensitivity and glycaemic control:

Castrated rats had poor glycaemic control in a background of insulin resistance as compared to sham rats. Testosterone replacement improved glycaemic control as well as insulin sensitivity of castrated rats. In castrated rats, insulin sensitivity improved on testosterone treatment as compared with placebo. The mean treatment effect and 95% confidence intervals of testosterone on the HOMA index was a reduction (−18.5, −46.3, −68.5%; p<0.05 respectively for 8, 16 and 24 mg/kg of testosterone) as compared with placebo (**Table 1**). This effect was explained by a parallel reduction in both fasting glucose (−4.5, −16.0, −37.8%; p<0.05 respectively for 8, 16 and 24 mg/kg of testosterone) and fasting insulin (−22.7, −40.1, −57%; p<0.05 respectively for 8, 16 and 24 mg/kg of testosterone) as compared with placebo (**Table 1**).

TABLE 1: GLUCOSE AND INSULIN RESISTANCE IN CASTRATED MALE RATS WITH AND WITHOUT TESTOSTERONE REPLACEMENT THERAPY

Parameters	Sham	Castrated (CC)	Testosterone replacement		
			8mg/kg	16mg/kg	24mg/kg
Glucose (mg/dl)	119 ± 15	156 ± 25*	149 ± 20#	131 ± 27	97 ± 10#
Insulin (µIU/ml)	2.3 ± 0.6	17.2 ± 3.2*	13.3 ± 0.6#	10.3 ± 1.1#	7.4 ± 0.8#
Insulin resistance	0. 9 ± 0.3	5.4 ± 1.3*	4.4 ± 0.5#	2.9 ± 0.4#	1.7 ± 0.1#

Sham: sham operated non castrated rats, CC: castrated control rats (8 weeks after castration), Castrated rats (8 weeks after castration) treated with Testosterone Enanthate 8 mg/kg (TRT 8) or 16 mg/kg (TRT 16) or 24 mg/kg (TRT 24).

Results were expressed as (Mean ± SEM), n= 6/group. *p < 0.05 CC vs. sham; #p < 0.01, treated rats vs. CC.

Lipid profile:

Castration induced an atherogenic lipid profile typified by lower HDL-C and higher levels of TC, LDL-C and TAG as compared to sham rats. Administration of testosterone replacement therapy, on the other hand, restored these changes in a dose response manner (**Table 2**).

TABLE 2: BLOOD LIPID PROFILES IN CASTRATED MALE RATS WITH AND WITHOUT TESTOSTERONE REPLACEMENT THERAPY

Parameters	Sham	Castrated (CC)	Testosterone replacement therapy		
			TRT 8	TRT 16	TRT 24
Total cholesterol (mg/dl)	79.6 ± 2.7	175.4 ± 5.2*	152.4 ± 6.2#	139.6 ± 2.3#	124.0 ± 4.3#
LDL-C (mg/dl)	39.6 ± 3.3	119.6 ± 4.9*	97.0 ± 6.2#	82.8 ± 3.6#	69.2 ± 4.8#
HDL-C (mg/dl)	33.4 ± 0.5	22.8 ± 1.3*	27.0 ± 1.6#	31.0 ± 1.4#	31.8 ± 1.3#
TAG (mg/dl)	40.8 ± 1.3	165.4 ± 4.8*	143.0 ± 6.8#	129.8 ± 1.9#	114.6 ± 3.8#

Sham: sham operated non castrated rats, CC: castrated control rats (8 weeks after castration), Castrated rats (8 weeks after castration) treated with Testosterone Enanthate 8 mg/kg (TRT 8) or 16 mg/kg (TRT 16) or 24 mg/kg (TRT 24). TAG – triglycerides; TC – total cholesterol; LDL-C – LDL-cholesterol: HDL-C – HDL-cholesterol.

Results were expressed as (Mean ± SEM), n= 6/group.*p < 0.05 CC vs. sham; #p < 0.01, treated rats vs. CC.

Serum CRP, IL-6, fibrinogen and endotheline-1:

CRP, IL-6, fibrinogen and endotheline-1 in castrated male rats were significantly ($p < 0.05$) higher than in sham rats. Testosterone replacement exerted a favourable effect on these parameters in a dose response manner (**Fig.2**).

Correlation analysis: Fibrinogen was positively correlated with many biomarkers used like endothelin-1 (r=0.6632, p<0.001), IL-6 (r=0.73, P<0.0001), CRP (r=0.71, P<0.0001), LDL-c (r=0.69, P<0.0001), HOMA-IR and negatively with HDL-c (r= -0.76, P<0.0001) as shown in **Fig.3**.

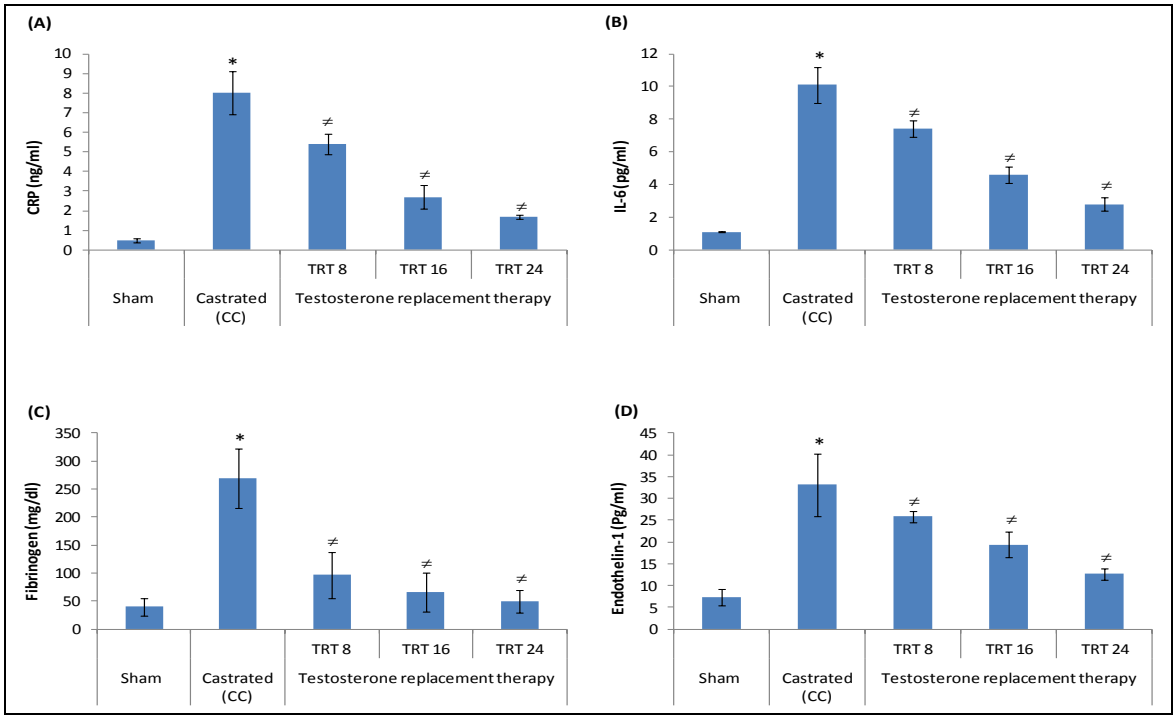

FIG. 2: SERUM CRP (NG/ML), IL-6 (PG/ML), FIBRINOGEN (MG/DL) AND ENDOTHELIN-1 (PG/ML) IN SHAM AND CASTRATED RATS (8 WEEKS AFTER CASTRATION) WITH AND WITHOUT TESTOSTERONE REPLACEMENT THERAPY. SHAM: SHAM OPERATED NON CASTRATED RATS, CC: CASTRATED CONTROL RATS (8 WEEKS AFTER CASTRATION), CASTRATED RATS (8 WEEKS AFTER CASTRATION) TREATED WITH TESTOSTERONE ENANTHATE 8 MG/KG (TRT 8) OR 16 MG/KG (TRT 16) OR 24 MG/KG (TRT 24).

Results were expressed as (Mean ± SEM), n= 6/group. *$p < 0.05$ CC vs. sham; $^{\neq}p < 0.01$, treated rats vs. CC.

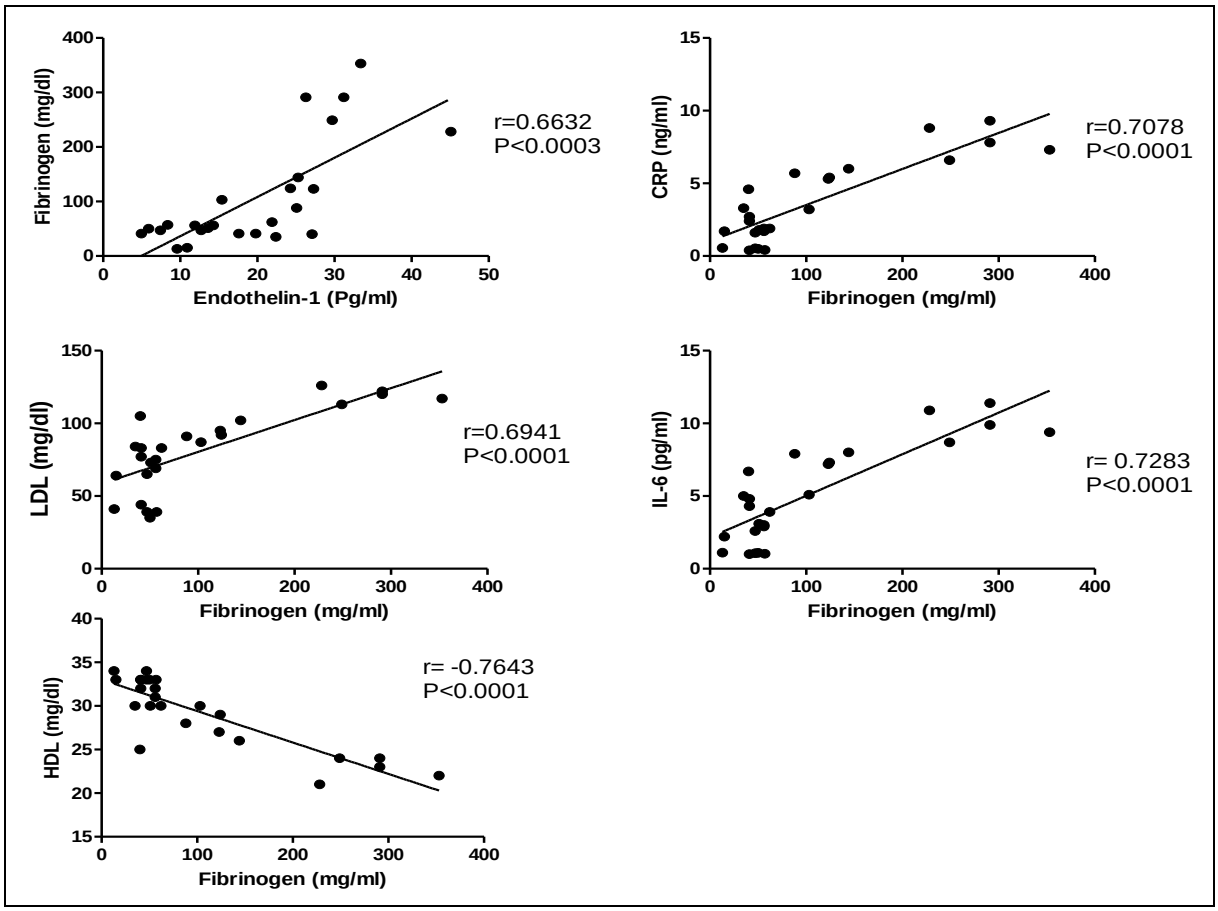

FIG.3: CORRELATION BETWEEN SERUM FIBRINOGEN AND OTHER PARAMETER STUDIED IN SHAM-OPERATED AND CASTRATED RATS WITH OR WITHOUT TREATMENT.

DISCUSSION: Present study demonstrated that castration of rats and almost complete depletion of serum testosterone has led to metabolic disturbance of carbohydrate and lipid profile. Insulin level additionally insulin resistance showed marked increase. These findings are in agreement with previous studies where total testosterone was reported to be inversely related to insulin concentration and its resistance in male individuals. Low testosterone levels are more common in diabetic patients. Clinical hypogonadism, on the other hand, is also associated with type 2 diabetes [6, 21]. Kapoor et al [21] reported significant improvements in insulin resistance, fasting glucose and HbA1c of diabetic hypogonadal men, treated with testosterone for three months [21].

Those authors suggested that testosterone treatment reduced triglycerides uptake by adipocytes due to the inhibitory activity of testosterone on lipoprotein lipase enzyme [22]. Therefore lower testosterone allows increase activity of lipoprotein lipase inducing increased fatty acid uptake and triglyceride storage in adipocytes along with an increase in fat mass which correlates with increased insulin resistance. Other potential mechanism is commonly attributed to the anti-inflammatory effect of testosterone which suppresses the cytokines, mostly involved in insulin resistance [23].

This is clearly evident in the present study where testosterone administration induced significant decrease in IL-6 and CRP. Androgen depletion due to castration of adult male rats demonstrated also marked changes in lipid profile where triglycerides, total cholesterol, LDL-c increased while HDL-c decreased as compared to sham groups and in agreement with others [24-27]. Many reported studies have characterized the initiation of the pro-atherogenic lipid profile in subsequent to testosterone deficiency [24-26].

Clinical studies illustrated that that normal men with low testosterone appear to have adverse lipid profile and hypogonadal men have a potentially atherogenic dyslipidemia [27]. On the contrary, few observational /cross-section studies have found no correlation between endogenous androgens and lipid profiles [28, 29].

The therapeutic effect of testosterone on HDL-c has been previously investigated in several studies showing differing results [30-32]. These conflicting findings may be explained by differences in the deposition site of adipose fat or levels of insulin sensitivity among patient groups or by the mode of testosterone administration (physiological versus supra physiological).

Decline of testosterone levels in aging men was attributed to the relative abundance of estradiol increases through increased aromatase activity [33, 34]. This usually leads to a general increase in body fat mass and could also explain the changes in lipid profile of hypogonadal men.

Clinical observations indicated that estradiol levels have been associated with the amount of circulating cholesterol [35, 36] and higher endogenous estradiol levels in men are associated with a more atherogenic lipoprotein particles profile [37]. Animal studies indicated that androgen-receptor deficient models suggest that testosterone mechanism to elevate HDL-c may be through conversion of testosterone to 17-β estradiol via aromatase and the subsequent activation of ER α- dependent pathways [38].

Castrated rats in the present study demonstrated marked increase in plasma fibrinogen and endothelin-1 levels turned to significantly decreased by testosterone treatment. The relationship between androgen deficiency, endothelial dysfunction and vascular disease is very complex. Insulin resistance which is exacerbated by androgen deficiency might mediate endothelial dysfunction and vascular disease [39]. Clinical consequences of insulin resistance include dyslipidemia [40], hyperglycemia [41], vascular inflammation and thrombotic risk inflammation [11,42].

Correlation coefficient showed positive relation between fibrinogen and many biomarkers used like endothelin-1, IL-6, CRP, LDL-c, MOMA-IR and negative one with HDL-c. Previous studies reported nearly similar findings where many cardiac medicines like fibrates, β-blockers, smoking cessation and physical exercise are associated with fibrinogen reduction.

CONCLUSION : Castration of rats resulted in propagation of many vascular risk factors like insulin resistance , inflammatory markers , endothelial dysfunction and atherogenic lipid profile . Administration of various dose levels of testosterone ,especially the medium one resulted in slow down expression of these risk factors which reflect the importance of androgens as a great prophylactic defense in the body.

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DECLARATION:

The authors declare that there is no conflict of interest that could prejudice the neutrality of the research reported.

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