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RESEARCH ARTICLE

ROLE OF TESTOSTERONE IN MODIFICATION OF ISCHEMIC HEART DISEASE

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ABSTRACT

The objective of this study was to assess the testosterone role in modification of ischemic heart disease. All subjects were male aged between 30 to 80 years. At the start of study, blood pressure, serum testosterone, lipid profile and left ventricular function were recorded. Males who were at high risk of cardiovascular disease have low endogenous testosterone level. The testosterone therapy, *250mg/2mlweekly* (Intramuscularly) for six months was sufficient to lower the risk of further cardiac complications by decreasing serum total cholesterol, low density lipoprotein and triglycerides levels ($p<0.0001$) and showed improvement in high density lipoprotein and serum testosterone levels ($p<0.02$). Moreover it has also ameliorated the Left Ventricular Function. The study concluded that exogenous testosterone may be considered a valuable addition as a regular therapy in Ischemic Heart Disease patients in order to codify their cardiac functions.

INTRODUCTION

Androgens may play a key role in gender difference; current researches are now investigating the mechanisms through which androgens affect morbidity, mortality and heart diseases. In history, estrogens are considered to be protective for cardiovascular system, as it was from the observation that women, on an average, live longer than men (Stamler, 1977). A large quantity of available information about testosterone effects earlier, showing a conflict in connection between decrease testosterone levels and cardiac disease, other studies showing entirely dissimilar ndings, presenting undeviating relationship among low testosterone levels and cardiac disease or death. Earlier data on hypogonadal males showed a connection with hormone levels and increased mortality (Shores *et al*., 2006). Testosterone is associated to numerous aspects of cardiovascular illness in males, but the precise role is unsure (Shabsigh *et al*., 2005, Haddad *et al*., 2007). The consequences of reduced androgen levels include fat mass gain, loss of muscle and bone mass, fatigue, depression, anemia, poor libido, and erectile dysfunction. Most of the studies in the medical literature have used a cutoff level of total testosterone of 300 ng/dl to aid in the biochemical diagnosis of hypogonadism (Rosner *et al*., 2007). The unswerving result of testosterone on coronary circulation in males is not known. In rabbits, testosterone administration has caused significant relaxation of pre-contracted aorta and coronary arteries in vitro, with or without endothelium (Webb *et al*., 1999). In vitro and in vivo studies have established that, testosterone have an impact on coronary vasodilation (Webb *et al*., 1999, Yue *et al*., 1995). A number of research groups have showed that testosterone therapy with I.M(Jaffe, 1977), I.V (Rosano *et al*., 1999), and transdermal preparations had animportant anti-ischemic effect in males with coronary disease (English *et al*., 2000c). Furthermore, men with coronary artery disease (CAD) have lower testosterone levels than men with normal coronary angiograms males of the same age (English *et al*., 2000b). Furthermore, it is evident from research studies that testosterone therapy delays the onset of ischemic heart disease (IHD), most likely as a consequence of a coronary vasodilator mechanism, improving the symptom of angina (English *et al*., 2000c, Samuel *et al*., 1943). Testosterone in men reaches highest levels at around the age of 30 years, after which levels gradually decline at a rate of 1 to

2% onyearly basis (Samuel *et al*., 1943). Levels of testosterone decrease in patients with persistent illnesses such as chronic obstructive pulmonary disease (COPD), human immunodeficiency virus, genetic disease like Klinefelter syndrome and type II diabetes mellitus (Cunningham *et al*., 2004, Kalyani *et al*., 2007). Acute illness, radiations, pituitary gland tumors are also known causes of low testosterone levels (Cunningham *et al*., 2004, Spratt *et al*., 1993). In men the progression and development of CAD is twice as compare to women (Stamler, 1977). One of the research study shows that men with decrease levels of serum testosterone are at higher risk of mortality secondary to cardiovascular disease in which the testosterone is less than the males with no cardiovascular disease and of same age(Barrett-Connor E, 1988). IHD progression can be reduced with the use of testosterone and there might be coronary vasodilator mechanism involved (English *et al*., 2000c).

Lipids levels always show different patterns with CAD. In particular in terms of high total low density lipoprotein (LDL) fractions, high total cholesterol, hyper triglyceridemia (Ramsay *et al*., 1996).There is an inverse correlation present between testosterone and obesity(Vermeulen *et al*., 1996, Vermeulen *et al*., 1999). Thus normal men with low testosterone appear to have adverse lipid profiles and a potentially atherogenic dyslipidemia before the treatment (Oppenheim *et al*., 1989). In the same way an inverse relationship is present between obesity and high density lipoprotein (HDL) (Lichtenstein *et al*., 1987).Testosterone is a key player in lowering of total cholesterol and LDL (Zgliczynski *et al*., 1996).The I/M testosterone therapy is also involved in decreasing the total cholesterol and LDL fraction in meta study of hypogonadal man having raised cholesterol and raised LDL fractions. In old age male patients, the testosterone is involved in ameliorating dyslipidemia and lowering of LDL levels related with atherosclerosis (Lancet, 1994). In malepatients with hypertension, the intensities of testosterone are low as compared to normal person(Phillips *et al*., 1993). Testosterone show to improve the cardiac output in patients with heart failure due to the result of reduction in peripheral vascular resistance therefore shows the property of vasodilation (Pugh *et al*., 2002).

Testosterone also shows an inverse relation with fibrinogen(DePergola *et al*., 1997, Phillips *et al*., 1994) and testosterone administration also results in the reduction of fibrinogen (Anderson *et al*., 1995). Testosterone also have an effect on haemostatic/fibrinolytic systems, it also shows anti-thrombotic activity and involve as a therapy in thrombotic diseases (Noll *et al*., 1985). Testosterone improves the condition of men suffering from chronic inflammatory disease after the testosterone therapy(NakhaiPour *et al*., 2007).A number of researchstudies investigate the relationship between serum total testosterone levels and all-causes of death.Statistically signi cant elevated rates of all-cause mortality in those men with decrease levels of endogenous total testosterone was found(Haring *et al*., 2010, Vikan *et al*., 2009, Tivesten *et al*., 2009, Laughlin *et al*., 2008). A key pathologic feature of congestive heart failure (CHF) is a metabolic shift toward catabolism, which results from the activation of neuroendocrine and in ammatory pathways (Anker *et al*., 1997b, Anker *et al*., 1997a). Emerging evidence shows that there might be a relationship between testosterone de ciency, CHF, and exercise capacity demonstrated that reduced levels of total and estimated free testosterone were both predictors of high mortalityrate in men with CHF (Jankowska *et al*., 2006).

MATERIALS AND METHODS

Study Participants

There were 60 patients of IHD who met the eligibility criteria of this study having ages in between 30-80 years. All the patients involved in this study were male hospitalized with a diagnosis of first incident of IHD.

Inclusion Criteria

All cases were selected according to the Council of Medical Research Study criteria of the Pakistan. Definite diagnosis of IHD was based on clinical examination, ECG readings, and capacity of left ventricular function (LVF). Research subjects were identified by visiting participating hospital, Chaudhary Pervaiz Elahi Institute of Cardiology (C.P.E.I.C)on daily or bi-weekly basis (two visits per week) and by consulting the physicians on duty.

Exclusion Criteria

- Diagnosed lung cancer and/or prostate cancer or prostate swelling
- Hemoglobin <10g/dl or >16.0g/dl
- Sleep apnea
- Drug abuse and Alcohol within the past year (based on self report)
- New York Heart Association, III or IV class CHF
- Myocardial infarction within the previous 03 months before entry
- Stroke within the previous 03 months before entry
- Chronic pulmonary disease
- Serumcreatinine levels>2.0mg/dL
- ALT 3x upper limit of normal
- Untreated depression and psychiatric disorders
- Medications use within the last three months:

1. Medication that have an effect on serum testosterone concentration
2. rhGH or megesterol acetate
3. daily use of prednisone for more than two weeks

- Antipsychotic medications for Axis I disorders
- Opiate abuse within the past 06 months

Subjects had a chronic kidney disease (CKD), liver disease, gastrointestinal tract or viral infection, HIV-infected, or thyroid disease. The data of expired patients were also excluded from the research project.

All the participants not only received the medicine prescribed by the doctor or group of doctors but also *Testosterone 250mg/2ml weekly* viaIM injection. All these subjects were interviewed on weekly or monthly basis about their dietary habits, intake of medicine, problems they face after being diagnosed from IHD, behavior, job or work, sexual behavior. During the research study, following tests were performed. These include Complete Blood Count, Serum Total Cholesterol, Serum Triglycerides, High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL), Serum Testosterone Levels, Left Ventricular Function test (LVF). These tests were carefully performed and records were maintained. The therapy of *Testosterone 250mg/2ml weekly* was extended further for

three months when improvement in health status in study subjects was seen.

Ethical Approval

This study was approved by Research and Ethics Committee (REC) of Faculty of Pharmacy, Hajvery University Lahore as well as Research and Ethics Committee of Ch-PervaizElahi Institute of Cardiology Multan. The study was approved by the committee and informed consent was obtained.

RESULTS

Only sixty male patients met the inclusion criteria. Their required tests were took and marked as baseline tests before the induction of exogenous test therapy. Some of the baseline test results are shown in Fig. 1 which describes the mean difference between the test results before the therapy, after three months and six months of therapy.

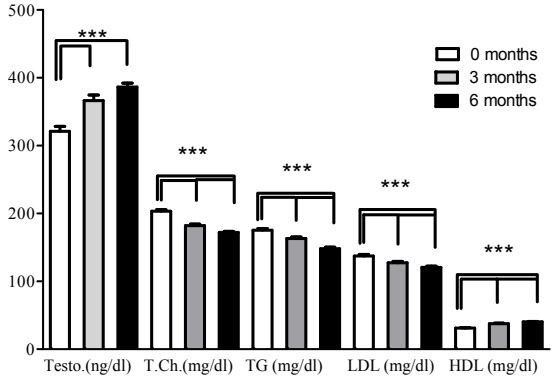

Fig. 1 Graphical representation of mean values

Fig. 1 is representing the significant improvement from mean baseline values of serum testosterone (Testo.), total cholesterol (T. Ch.), triglycerides (TG), Low density lipoprotein (LDL) and high density lipoprotein (HDL) after receiving exogenous testosterone 250mg/week therapy after three months of therapy and six months of therapy of testosterone.

The test results showed that the patients with IHD had testosterone level below normal range which may be a marked sign of disturbing other test results such as serum total cholesterol, serum Triglycerides, serum LDL, serum HDL, most importantly the LVF and may cause further complications if not addressed.

Themean baseline serum testosterone level is 321ng/dl. The serum testosterone level after three months of therapy was 366ng/dl and 386ng/dl after the therapy extended for three more months as shown in Fig. 2.

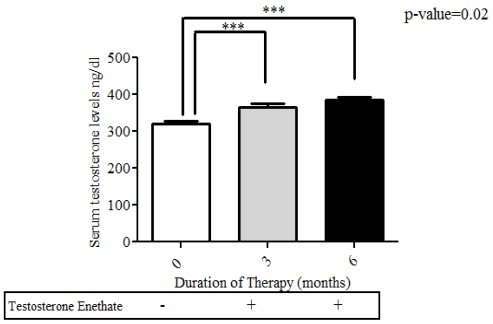

Fig. 2 Serum testosterone levels (One-way ANOVA with RM)

Fig. 2 is showing the comparison of baseline testosterone levels and the improvements of serum testosterone levels after induction of exogenous testosterone for three months and six months of therapy (p<0.02).

As well as the condition of the patients perked up especially in elderly patients above sixty years of age. Exogenous testosterone induction as an adjunct therapy not only enhanced the serum testosterone levels but also the physical ability of the patients (p<0.02). Baseline total cholesterol levels were towards higher range as depicted in Fig. 3.

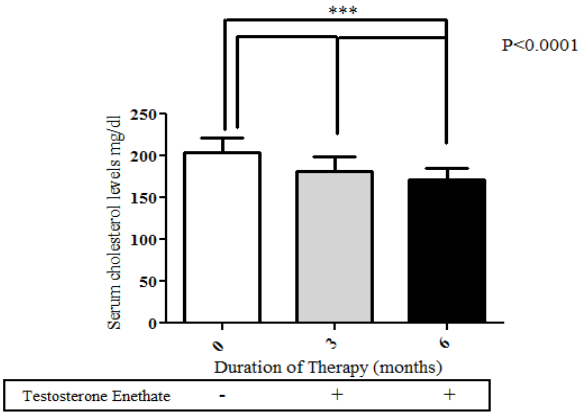

Fig. 3 Serum cholesterol levels (One-way ANOVA with RM)

Fig. 3 is representing the relationship between baseline serum total cholesterol, cholesterol level after three months and six months extended therapy (p<0.0001).

But after the introduction of experimental intervention, it was found that the serum total cholesterol level got better and there was a decreasing trend of cholesterol level after three months of therapy and extended six months of therapy(p<0.0001).

The ameliorations in baseline serum triglycerides levels after the therapy of three months and significant improvement after the therapy extended for further three months (p<0.0001) were observed in Fig. 4.

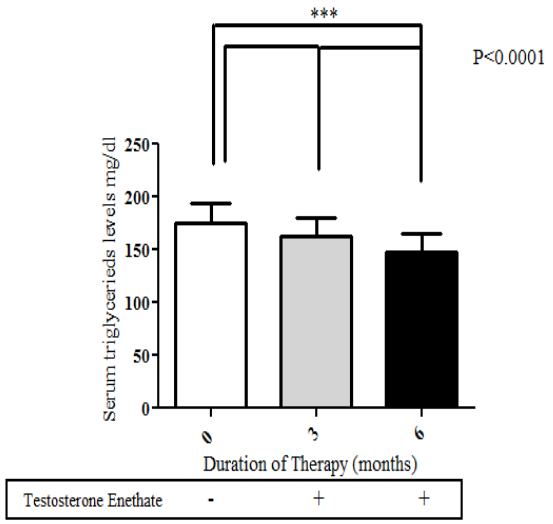

Fig. 4 Serum triglycerides levels (One-way ANOVA with RM)

Fig. 4 shows the comparison between the baseline serum triglycerides before the exogenous testosterone therapy shown in white column, after three months shown in gray column, and six months therapy in black column (p<0.0001).

In comparison to the baseline serum LDL, the induction of exogenous testosterone as adjunct therapy shows much more significant result and improvement in the serum LDL as is shown in Fig. 5.

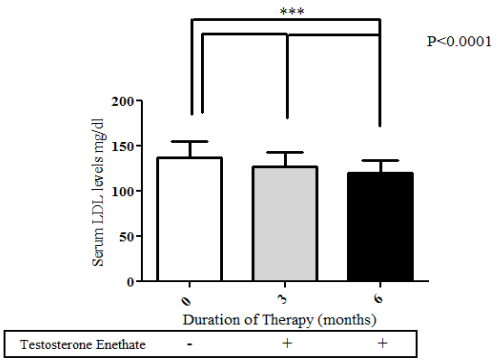

Fig. 5 Serum LDL levels (One-way ANOVA with RM)

Fig. 5 illustrates the difference between the base line serum LDL levels in white column, and improvements in the serum LDL levels after three months shown in gray column and six months therapy shown in black column (p<0.0001)

The serum LDL levels were decreased comprehensively as compared to baseline results (p<0.0001). On one hand the exogenous testosterone was able to decrease the serum LDL levels and on the other hand the serum HDL level raised as shown in Fig.6 as compared to baseline serum HDL after three months of therapy.

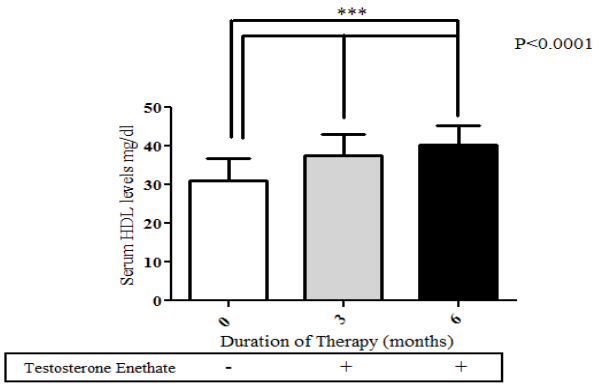

Fig. 6 Serum HDL levels (One-way ANOVA with RM)

Fig. 6 demonstrates the difference between the base line serum HDL levels in (white column) before the induction of exogenous testosterone therapy and improvements in HDL after three months (gray column) and finally improvements in the serum HDL levels (Black Column) after six months therapy through statistical analysis (p<0.0001).

After six months more marked improvements resulted (p<0.0001). The baseline LVF test results showed poor values as shown in Fig. 7.

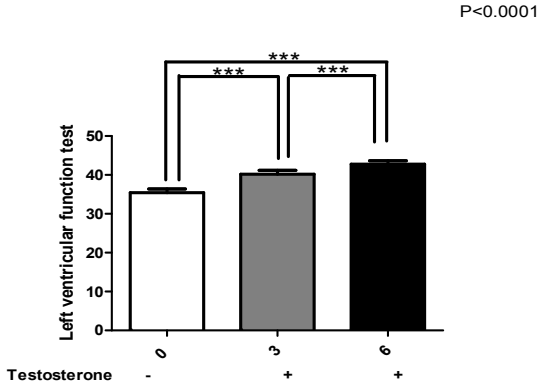

Fig. 7 Left Ventricular Function (One-way ANOVA with RM)

Fig. 7 describes the significant amelioration (p<0.0001) in the base line LVF (Left ventricular function). White column is representing the value at the start of therapy, (Gray column) after three months and (Black column) at the end of six months therapy.

In most of the patients the LVF function was quietly disturbed and below normal readings obtained but after incorporation of exogenous testosterone for three months, the LVF results were improved. Extension of therapy for further three months showed significant improvements in LVF results (p<0.0001).

DISCUSSION

The concept increasing in support of the fact that is an inverse relationship is present among low levels of serum testosterone and cardiac problems specially IHD and CAD. The males which had lower levels of endogenous testosterone are prone to develop CAD, IHD and disturbed lipid profile(Rosano *et al*., 2007, Li *et al*., 2012, Phillips *et al*., 1994).Serum testosterone level was lower in enrolled IHD patients of our study and this is in line with previous reports showing that testosterone confers cardiovascular protection by direct action on myocardium(Tsang *et al*., 2007). Administration of testosterone increases cardiac output acutely apparently via reduction in left ventricular after load(Pugh *et al*., 2002).Owing to anabolic properties, testosterone is also known to act as a vasodilator in systemic, coronary and pulmonary vascular beds (Tep-areenan *et al*., 2002, English *et al*., 2000a, English *et al*., 2002, English *et al*., 2001, Jones *et al*., 2002). Testosterone has been used as add on therapy in men with CHF that showed useful effects in them(Shapiro *et al*., 1999). In laboratory rats, testosterone therapy increases coronary blood flow and improves both partial and peak oxygen consumption by myocardium (Scheuer *et al*., 1987).

The effect of testosterone was not previously tested in humans with IHD and altered LVF. During this study a significant improvement in LVF during and after testosterone therapy has been observed in patients. High cholesterol levels have always shown to be one of the most imperative risk factors for the advancement towards atherosclerosis. Research studies have shown that men are at increased risk of developing adverse lipid pro les (Whitsel *et al*., 2001), and experience the risk of cardiovascular disease mortality more commonly as compared to women of similar age (Calof *et al*., 2005). The research studies linking the relationship between baseline serum testosterone levels and different lipid profiles and sub fractions having conflict, and therefore a clear agreement have not been accomplish by the various authors who have investigating this association also. Large, potential, population-based studies are required to further explain this matter. The proof on the effect of exogenous testosterone therapy lipid sub fractions levels is likewise different in different research studies. In one of the research study the exogenous testosterone replacement therapy through intra muscular injections cause a small amount of decrease in total serum cholesterol levels (Corona *et al*., 2011). Previously it was claimed generally through research studies that higher level of testosterone is the major cause of prostate cancer in male patients. The results of some clinical studies contradict that the exogenous testosterone administration is directly related to increase the risk of developing the prostate cancer in male patients receiving the exogenous testosterone. One of the research study showed that there were an increase prostate-related undesirable proceedings with exogenous testosterone administration (Filippi *et al*., 2009).

As a major androgenic hormone in males the testosterone also produces its effect in maintaining the body mass index of person. The precise mechanism by which endogenous testosterone and fatness is relate to each other is still not known. Testosterone may cause the breakdown of abdominal

fats in adipose tissue, which results in the reduction of fat in abdominal area of the body. Exogenous testosterone therapy produced some beneficial effects by lowering fats of the body. Thus by doing this, preventing the increase in fats of the body and ultimately providing safety from cardiac problems in future(Alexandersen *et al*., 1999). Another study shows the same and prosperous result in animal model. This discovery was con rmed in animal models as well(Godsland *et al*., 1987).

The impact of exogenous testosterone administration is helpful in maintaining the levels of serum testosterone levels in men with IHD. If there will a reduction in cholesterol availability there will be a less production of testosterone and the other function of human body might be affected with this preposition. The most important in lowering the male testosterone levels is the use of 3-hydroxy-3-methylglutaryl-Coenzyme A reductase inhibitors which not only decrease the total cholesterol, triglycerides, low density lipoproteins but they indirectly effect the production of sex hormones in male and thus not only effecting the production of testosterone but effecting other levels whose regulation are attributed to testosterone function in males. In one of the research study on exogenous testosterone therapy showed that testosterone replacement therapy improve the total serum cholesterol levels as compared to the testosterone levels before starting the therapy(Corona *et al*., 2011).

Our research study is advocating the IM administration of testosterone (250mg/2ml/week) as it is helpful in lowering the serum total cholesterol in IHD patients (Fig. 3). The mean of baseline cholesterol level shows decreasing trend after three months of testosterone therapy and more prospective results were seen as this therapy continued for three more months and at the end of therapy, we have better results and there was more improved and controlled total cholesterol levels. Patients show more positiveness towards the therapy and results are more influencing.

The improvements in the baseline serum triglycerides levels of IHD patients were also found when exogenous testosterone incorporated. The baseline results of patient shows high range patterns of serum Triglyceride levels. When these patients received exogenous testosterone for three months there was improvement in total cholesterol and Triglyceride levels. A further reduction in Triglycerides levels was observed when testosterone therapy proceeded for next three months and after six months there were marked improvement in results as shown in the (Fig. 4). This shows that testosterone is multifunctional hormone.

In low (LDL) cholesterol receptor de cient mice, orchiectomy is associated with accelerated formation of atherosclerotic lesions in the aorta, and testosterone supplementation was shown to retard the progression of these lesions(Nettleship *et al*., 2009). Administration of an aromatase inhibitor blocked the bene cial effects (Nathan *et al*., 2001). The LDL cholesterol levels decreases after exogenous testosterone replacement therapy(Nettleship *et al*., 2009).

The significant reduction in LDL levels in Chinese men were seen when testosterone was administered via IM route after four weeks for 3 months. They found that the effect of exogenous Testosterone on LDL activity is transient because of the multiple peaks and troughs of testosterone that are produced when testosterone is administered exogenously, causing a down regulation of LDL. The decreased levels in LDL-C (low density lipoprotein-chylomicrons) size, however, persisted to the end of the study(Zhao and Li, 1998). These results are in conjunction with our findings. In our research the testosterone therapy shows prospective improvements not only in serum total cholesterol, Triglycerides, HDL but also shows improvement in serum LDL levels (Fig. 5).

Testosterone has some major effects on HDL concentration. Testosterone caused significant development in HDL levels. Fig. 6 shows the result of effectiveness of testosterone on HDL. After the baseline test, the therapy was introduced. Three months therapy produced better results than without therapy so we continued the therapy for next three months (Fig. 6) and observed further improvement in HDL data at the end of therapy. One of the research studies shows marked improvement in LDL levels and moderate improvements in HDL levels when participants receive testosterone therapy on weekly basis. It means that there is an inverse relationship present between the LDL and HDL. So if LDL decreases the HDL increases (Tsang *et al*., 2007). The LVF is mainly disturbed in patients suffering from IHD. Introduction of exogenous testosterone also plays its part in improving LVF (Pugh *et al*., 2002). There are some indications which shows that exogenous testosterone is growing evidence suggesting that testosterone might take part in the regulation of ventricular repolarization (Calof *et al*., 2005). In our research study the patients with IHD had deceased LVF state. When testosterone was introduced in their therapy, there are marked developments in LVF status and effect of exogenous testosterone therapy has caused remarkable improvement in LVF after six months of therapy (Fig. 7).

The results of this research study have significance because testosterone is the most important androgenic hormone of males differentiating them from females and improved the cardiac health status of study subjects. These outcomes may establish a solid ground for future studies addressing the cardiac problems in male. Advance research studies required to examine the effects of long-term, dose dependent exogenous testosterone administration in men with IHD or CAD and risk factors for CAD in men.

CONCLUSION

Androgenic hormone plays a key role in maintaining and improving the health of males' especially cardiac health. This study shows that exogenous testosterone improves cardiac health and lipid profile in males which plays an integral role in maintaining cardiac health. Furthermore this study also highlights that exogenous testosterone can improve myocardial ischemia, left ventricular function and lasting out come in men with established ischemic heart disease.

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