"ASSOCIATION BETWEEN TESTOSTERONE LEVEL AND CORONARY ARTERY DISEASE"

Dissertation submitted to

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY

In partial fulfilment of the

Regulations for the award of the degree of

(M.D. PHYSIOLOGY)

BRANCH-V

THANJAVUR MEDICAL COLLEGE HOSPITAL

THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERISTY

CHENNAI, INDIA

APRIL – 2017

CERTIFICATE

This dissertation entitled **"ASSOCIATION BETWEEN TESTOSTERONE LEVEL AND CORONARY ARTERY DISEASE "** is submitted to The Tamil Nadu Dr.M.G.R. Medical University, Chennai in partial fulfillment of the regulations for the award of M.D., Degree in Physiology in the Examinations to be held during April 2017.

This Dissertation is a record of fresh work done by the candidate Dr.J.B.ASHRAF ALI, during the course of the study (2014-2017). This work was carried out by the candidate himself under my supervision.

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DECLARATION

I solemnly declare that the Dissertation titled **"ASSOCIATION BETWEEN TESTOSTERONE LEVEL AND CORONARY ARTERY DISEASE"** is done by me at Thanjavur Medical College, Thanjavur

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CERTIFICATE

Approval No.: 114

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submitted by Dr. .....T.B. ASHRAF ALI..... **of**

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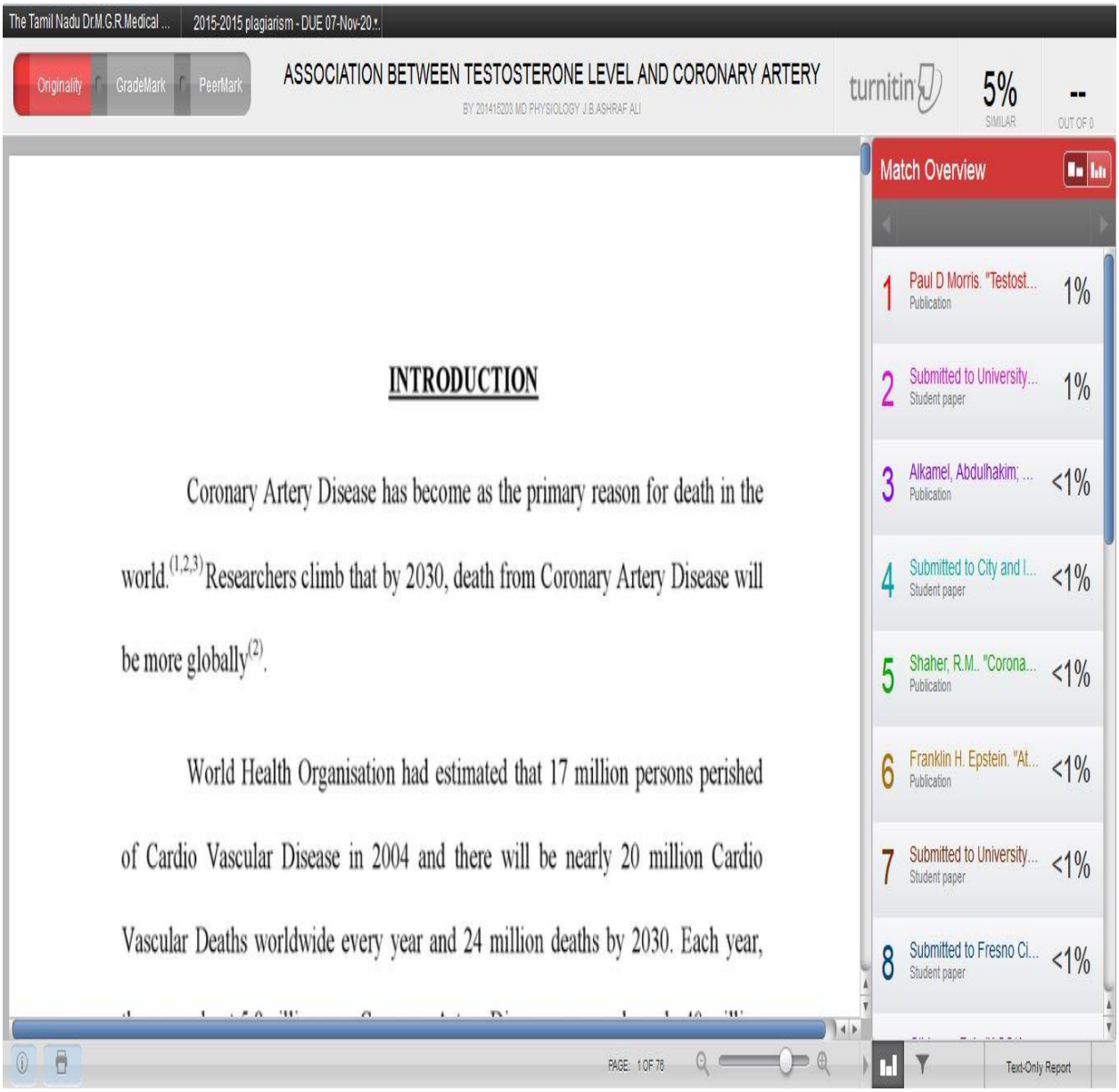


CONTENTS

“ASSOCIATION BETWEEN TESTOSTERONE LEVEL AND CORONARY ARTERY DISEASE”

INTRODUCTION

Coronary Artery Disease has become as the primary reason for death in the world.[1,2,3] Researchers climb that by 2030, death from Coronary Artery Disease will be more globally[2].

World Health Organisation had estimated that 17 million persons perished of Cardio Vascular Disease in 2004 and there will be nearly 20 million Cardio Vascular Deaths worldwide every year and 24 million deaths by 2030. Each year, there are about 5.8million new Coronary Artery Disease cases and nearly 40 million persons with established Coronary Artery Disease are living today.[3]

Testosterone is the principal androgen in the circulation, which is synthesized and secreted mainly by Leydig cells.[4,5] Testosterone effects include vasodilatation[4,6] and amelioration of coronary ischemia and also potentially deleterious effects.[4]

It is broadly acknowledged that men encounter a steady drop in their level of testosterone along with increasing age, and male sex for a long time viewed as a strong threat feature for developing Coronary Artery Disease. Altogether, these two details have driven various researchers to seek for a probable correlation among endogenous testosterone concentration and Coronary Artery Disease.[7]

The rapid vasodilatory impact of testosterone concentration on the Ischemic Myocardium in patients suffering from Coronary Artery Disease is credited to a direct non genomic outcome of androgens on vascular cells.[8]

Hypogonadism is associated with the increased level of blood sugar, increased level of triglycerides, high body mass index, high waist to hip ratio, increased total body fat mass, increased fasting insulin resistance index which are all the risk factor for developing Cardiovascular Disease.[9]

Risk factors of Cardiovascular Disease, which may be influenced by Testosterone includes Vascular tone, Serum Lipoprotein profile, Platelet count, Red Blood Cell counts and the development of Atherogenesis. Most epidemiological studies states that higher serum Testosterone levels corresponds with lesser Cardio Vascular Disease threat in men.[9]

Testosterone affects the arterial wall - Prostaglandin system, which favours the vasoconstriction and platelet aggregation when there is thrombaxane formation.[6]

Emerging evidences indicates a crucial part of androgens in cardiovascular health of men. In this study, we demonstrate that whether or not serum testosterone concentration in men who have Coronary Artery Disease is lesser than the Normal Coronary Vasculature.

AIMS AND OBJECTIVES

- To evaluate the difference between the Plasma Sex Hormone and Coronary Artery Disease in patients undergoing Coronary Angiography and in matched controls.

- To determine whether levels of androgens vary among the men with and men without Coronary Artery Disease.

REVIEW OF LITERATURE

ANATOMY OF CORONARY ARTERIES

The heart obtains their blood supply through two major coronary arteries normally. The Right branch of the coronary artery generally provides the right ventricle and atrium and the Left branch of the Coronary Artery provides the left ventricle and atrium arising from the ascending aorta from its anterior and left posterior sinuses.[10]

ANATOMY OF CORONARY ARTERIES

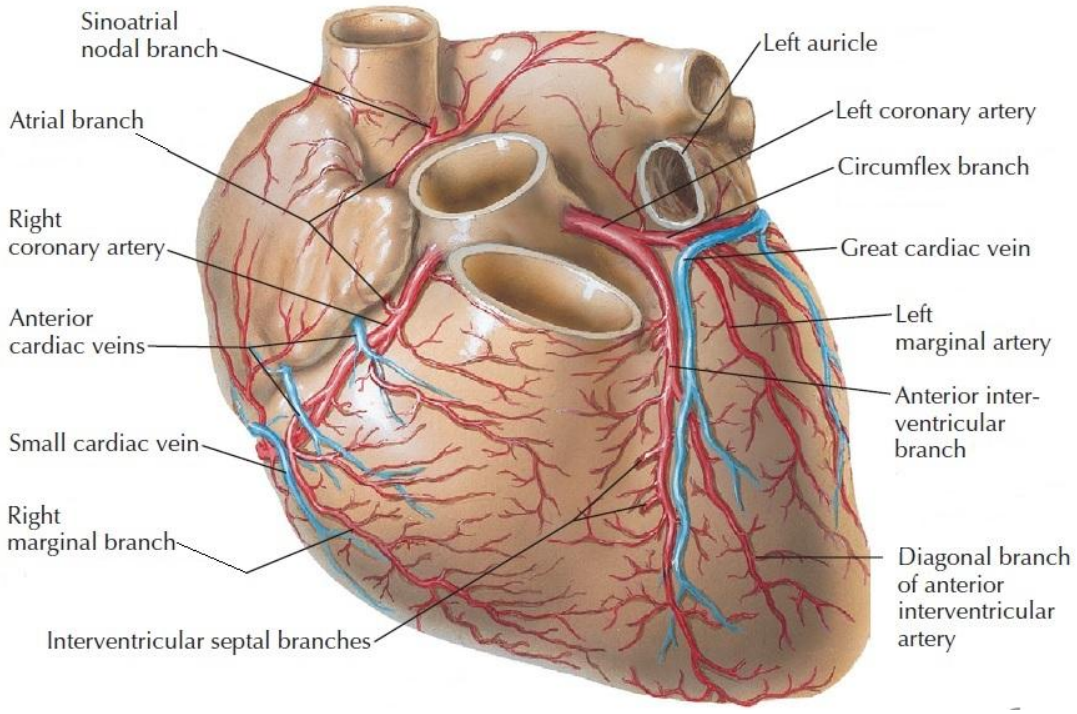


FIGURE 1

LEFT CORONARY ARTERY:

Left sinus of Valsalva nearby its upper border gives rise to the left coronary artery (LCA), at about the level of the open border of the valve cusp. The LCA has a short (0.5-2 cm) common stem that bifurcates or trifurcates usually.[10,11]

First branch, the anterior interventricular (descending) branch, courses downward in the anterior interventricular groove which is largely embedded in thick fat, which encircles the acute border of the heart just to the right side of the apex, and ascends up to the posterior interventricular groove. The left anterior descending branch of the LCA provides branches to the adjacent side of the anterior Right Ventricular wall which usually anastomose with branches from the right coronary artery and septal branches which supply anterior two thirds and apical portions of septum, and also supplies the number of divisions to the anteroapical segments of the left ventricle, which includes the anterior part of the papillary muscle. One of the septal branch originating from the upper third of the anterior interventricular branch is usually larger than the others, which gives nutrients to the midseptum, and also the bundle of His and the conductive system of the branches of the bundle. This branch also may supply the anterior part of the papillary muscle of right ventricle through moderator band.[10]

The second branch of the left coronary artery is the smallest circumflex branch which passes through the left AtrioVentricular sulcus. It branches off to the upper lateral portion of the left ventricular wall and to the left atrium. The circumflex branch usually terminates at the obtuse margin of the heart, but it can

reach the crux which is the junction of posterior interventricular sulcus and posterior AtrioVentricular groove. If the circumflex branch reaches the crux, it supplies the entire left ventricle and the septum of the ventricles, with or without the right coronary artery.[10]

The Third branch, if LCA trifurcates, coming off amongst the anterior interventricular branch and the circumflex branch, is merely an Left Ventricle branch that originates from the main artery.

RIGHT CORONARY ARTERY:

The right anterior sinus of Valsalva of the aorta gives rise to the right coronary artery (RCA), which passes besides right AtrioVentricular sulcus. The right coronary artery encircles the acute border to get into the crux in the majority of cases. It branches off to various amount to the anterior side of the Right Ventricle wall. The posterior interventricular descending branch move downwards along with the posterior interventricular groove, and provides nutrients to the posterior third of the interventricular septum. The diaphragmatic part of the right ventricle is largely supplied by small, parallel branches from the marginal and posterior descending arteries, and not from the parent vessel itself. [10,11]

Commonly, the posterior papillary muscle of the left ventricle have double blood supply from left and the right coronary artery. Of the right atrial divisions of right coronary artery, one is of great importance. This branch originates from the RCA shortly after its takeoff and ascends along the right atrium on the anteromedial border. It enters through the upper part of atrial septum, reappears as

the superior vena cava branch as nodal artery, posterior and to left side of the Superior Vena Cavae ostium, rounds the ostium which runs closer towards the sinoatrial node, and providing the branches off to the crista terminalis and pectinate muscles.[10]

BRANCHING PATTERN VARIATIONS

In Human Heart, variations in the branching pattern are extremely common. In aound 67% of the cases, the Right Coronary Artery transverses the crux and provides portion of the Left Ventricular wall and the septum of the ventricules. Over 15% of cases, as seen in dogs and many other mammals the LCA circumflex branch passes the crux, by giving away the posterior interventricular branch, which providing the entire left ventricle, the ventricular septum, and portion of the RV wall. Over 18% of cases, together both coronary arteries access the crux. No real posterior interventricular branch may exist, but the posterior septum is penetrated at the posterior interventricular groove by many branches from the LCA, RCA, or both. In about 40% of cases the SVC branch is a continuation of a large anterior atrial branch of the LCA rather than of the anterior atrial branch of the RCA. [10]

Also, the first branch of the RCA may originate independent of the right sinus of Valsalva rather than from the parent artery. Rarely, the second or even the third RCA branch arises independently.[10,11]

CORONARY DOMINANCE:

Coronary Dominance refers to the Coronary Artery which branches off the Posterior Interventricular Artery. Right dominance occurs when the

posterior interventricular artery emerge after the right coronary artery which is 80%. Left dominance occurs when posterior interventricular artery arises from left coronary artery which is 10%. Co-Dominance occurs when the posterior interventricular artery is moulded together with both right and left coronary arteries which is 10%.[12]

CORONARY VEINS:

Most of the coronary veins enter the coronary sinus. The three largest veins are the great cardiac, middle cardiac and posterior left ventricular vein. The Ostia of these veins may be guarded by fairly well developed unicuspid or bicuspid valves. The oblique vein of Marshall of the left atrium enters the sinus near the orifice of the great cardiac vein. Its ostium never has a valve. Independently, the right atrium receives the small cardiac vein and the anterior cardiac veins always do. Small venous systems in the atrial septum and probably in ventricular walls and septum enter the cardiac chambers directly, called the thebesian veins.[11]

CORONARY CIRCULATION

The circulation of the coronary system is exceptional as they are accountable to produce the arterial pressure as it is necessary to perfuse the systemic circulation on the whole and also has its own perfusion impeded during the cardiac cycle.[13]

Although, Heart is less than that of 0.5% of total body weight, it obtains around 5% of the cardiac output at rest. The heart normally uses oxidative phosphorylation to generate the ATP required to pump blood. However, of all the

oxygen that the heart consumes, no more than 40% reflects the oxidation of carbohydrate, remaining 60% of myocardial oxygen consumption in the fasting state is due to the oxidation of fatty acids. The myocardium readily oxidizes ketone bodies, which can provide considerable energy throughout starvation or DiabeticKetoAcidosis. When the Oxygen supply is adequate, the heart oxidises both lactate and pyruvate, as do red skeletal muscle fibres, although the arterial concentration of pyruvate is usually low.[14]

Contraction of the Myocardium is directly related to the oxygen supply. The stability involving both oxygen demand and oxygen supply is the vital risk marker for the function of the heart.[13]

When the energy demand for ATP exceeds the supply of Oxygen by diseases affecting coronary blood flow, the heart can no longer take up lactate but instead releases lactate by breaking down its own glycogen stores. In this manner, the heart can continue to function for a short time when it is deprived of O2. Nociceptive fibres triggers the sense of referred pain, if there is hypoxia in the myocardium, which is known as angina pectoris. Prolonged or more severe insult of the myocardial tissue, results ultimately in necrosis, which is known as myocardial infarction. This precipitates a vicious cycle, in which ischemia-provoked contractile dysfunction, that further attenuates hypotension and further ischemia.[13,14]

The branches of Left Coronary artery course on top of the heart, branching into segments that penetrate into the tissue and dividing into capillary networks. Capillary density in histological sections of the human heart exceeds

3000/mm2 as skeletal muscle has only 400/mm2. The small diameter which is <20 μm of cardiac muscle fibres is lesser than the skeletal muscle which is 50 μm. The cardiac muscle fibres facilitates O2 diffusion into the cardiac cells, which have a high energetic demand.[5]

Once blood passes through the capillaries, it collects in venules, which drain outward from the myocardium to converge into the epicardial veins. These veins empties in right atrium by the coronary sinus. Other vascular channels drain directly into the cardiac chambers which includes the thebesian veins. Because the deoxygenated blood carried by the thebesian veins exits predominantly into the ventricles, this blood flow bypasses the pulmonary circulation. Numerous collateral vessels among branches of the arterial vessels and throughout the venous system act as anastomoses. These provide alternative routes for blood flow when a primary vessel become occluded.[10,14]

EXTRAVASCULAR COMPRESSION:

In systemic circulation, blood flow roughly parallels the pressure grade in the aorta, rising in systole and falling in diastole. But, in the coronary circulation, flow is somewhat paradoxical. Although the heart is the source of its own perfusion pressure, myocardial contraction effectively squeezes its own blood flow. Hence, the profile of vascular supply by coronary arteries is mainly dependent on the aortic perfusion pressure and the extra vascular compression resulting from the contracting ventricles, particularly the left ventricle.[14]

In the left coronary artery, transiently blood flow may actually reverse in early systole as the force of the left ventricle's isovolumetric contraction compresses the left coronary vessels, while the aortic pressure has not yet begun to rise as aortic valve is still closed. As aortic pressure increases later during systole, coronary blood flow increases but never reaches peak values. However, early during diastole, when the relaxed ventricles no longer compress the left coronary vessels and aortic pressure is still high, left coronary flow rises rapidly to extremely high levels. Around 80% of total left coronary vascular supply strikes during diastole.[14]

Contrastingly, the profile of vascular supply by way of the right coronary artery matches the pressure profile of its feed vessel, the aorta. Here, systole contributes a greater proportion of the total flow, and systolic reversal does not occur. The reason for this difference is developed by the right side of the heart because of the lower wall tension, as it pumps against lower resistance of the pulmonary circulation and does not occlude the right coronary vessels during contraction. At the onset of lethal arrhythmia, left coronary perfusion briefly raises, which reflects the loss of mechanical compression of vasculature. Due to the variation in the heart rate, the duration of diastole more than the systole is affected and also affects the coronary flow. In the course of tachycardia, the fraction of the cardiac cycle spent in diastole decreases, minimizing the phase accessible for utmost left coronary perfusion. If the heart is healthy, the coronary vessels can adequately enlarge in reaction to the metabolic signals caused by increased cardiac work, which offsets the negative outcome of the shorter diastole. Conversely, an increased heart rate can be risky when severe coronary artery disease limits blood flow. Coronary

vascular supply alters in time during the cardiac cycle and it also alters along with depth in the heart wall. Blood flows to myocytes of the heart through arteries that penetrate from the epicardium in the direction of endocardium.[14]

The intramuscular pressure is more aound the endocardium and less around the epicardium during the systole. All things being equal, the perfusion of the endocardium would therefore be less than that of the epicardium. However, total blood flows to the endocardial and epicardial halves are approximately equal, as the endocardium has a lesser intrinsic vascular resistance. Hence there is increased blood flow during diastole. When the diastolic pressure at the aortic root is pathologically low or coronary arterial resistance is high, endocardial blood flow falls below the epicardial flow. Thus, the inner wall of the left ventricle often experiences the greatest damage with atherosclerotic heart disease.[14]

MYOCARDIAL METABOLISM:

Coronary circulation has a striking mark, which is the nearly linear connection amongst oxygen consumption of myocardium and myocardial vascular supply. In a resting individual, each 100 g of heart tissue receives 60 to 70 mL/min of vascular supply. Normally, the myocardium takes out 70% to 80% of the oxygen of arterial blood which is normally 20 mL/dL blood, thereby producing an extremely low venous O2 content which is 5 mL/dL. Therefore, the heart may not react in response to bigger metabolic demands by taking out much more oxygen than it already has, when the individual is at rest. The heart can meet large increases in O2 demand only by increasing coronary blood flow, which can exceed 250 mL/min per 100 g with exercise. Because blood pressure normally varies within fairly narrow

limits, the only way to substantially increase blood flow through the coronary circulation during exercise is by vasodilatation. The heart relies primarily on metabolic mechanisms to increase the calibre of its coronary vessels. **Adenosine** has received particular emphasis in this regard. A rise in the metabolic action of the myocardium, which results in deficit of the coronary blood flow or drop in the myocardial PO2, which results in adenosine release. Further, Adenosine diffuses into the Vascular Smooth Muscle Cells, stimulating purinoceptors to provoke vasodilatation by means of decreasing [Ca2+]i. Thus, inadequate perfusion to a region of tissue would elevate interstitial adenosine levels, which causes vasodilatation and restore the blood flow to the affected region.[14]

When cardiac demand outstrips the blood supply, a brief increase in [K+]o, may play a vital role for the initial rise in coronary perfusion. However, it is unlikely that K+ mediates sustained elevations in blood flow. When oxygen demand overrides oxygen supply, the increase in the PCO2 and the decrease in PO2 lowers the coronary vascular resistance.

Coronary vascular supply is relatively stable between perfusion pressures of 70mm Hg and more than 150 mm Hg. Thus, like that of the brain, the blood flow to the heart exhibits auto regulation. In addition to the myogenic response which contributes to the coronary auto regulation, fluctuations in adenosine and PO2 also plays an important role.[14,15]

SYMPATHETIC STIMULATION:

Sympathetic nerves follows the arterial supply, coursing throughout the heart. Stimulation of these nerves causes the heart to beat more frequently and more

forcefully. β1 Adrenoceptors on the cardiac myocytes mediate these chronotropic and inotropic responses. As discussed in the previous section, the increased metabolism of the myocardium leads on to coronary vasodilatation through metabolic pathways. However, during pharmacological inhibition of the β1 receptors on the cardiac myocytes, which prevents the increase in metabolism, sympathetic nerve stimulation causes a coronary vasoconstriction. This response is the direct effect of sympathetic nerve action on α adrenoceptors of the coronary resistance vessels. Thus, blocking of β1 receptors exposes adrenergic vasoconstriction. But, under normal circumstances, the tendency of the metabolic pathways to vasodilate far overwhelms the tendency of the sympathetic pathways to vasoconstrict.[14,15]

Stimulation of the vagus nerve has merely a weak vasodilatory effect on the coronary resistance vessels. This muted response is not due to insensitivity of the resistance vessels to acetylcholine, which elicits a pronounced vasodilatation when it is administered directly. Rather, the release of acetylcholine from the vagus nerve is restricted to the vicinity of the sinoatrial node. Thus, the vagus nerve has a much greater effect on heart rate than on coronary resistance.[14,15]

COLLATERAL VESSEL GROWTH:

When a coronary artery or one of its primary branches becomes abruptly occluded, ischemia can produce necrosis (i.e., a myocardial infarct) in the region deprived of blood flow, as discussed earlier. However, if a coronary artery narrows gradually over time, collateral blood vessels may develop and at least partially ameliorate the reduced delivery of O2 and nutrients to the compromised area, preventing or at least diminishing tissue damage. Collateral vessels originate

from existing branches that undergo remodelling with the proliferation of endothelial and smooth muscle cells. Stimuli for collateral development include angiogenic molecules released from the ischemic tissue and changes in mechanical stress in the walls of vessels supplying the affected region.[14]

CORONARY STEAL:

A variety of drugs can promote vasodilatation of the coronary arteries. These are typically prescribed for patients suffering from angina pectoris, the chest pain associated with inadequate blood flow to the heart. If the build-up of atherosclerotic plaque, which underlies angina pectoris—occurs in the large epicardial arteries, the increased resistance lowers the pressure in the downstream micro vessels. Under such conditions, the physician should be cautious in using pharmacological agents to dilate the coronary vessels. In an ischemic area of the myocardium downstream from a stenosis, metabolic stimuli may have already maximally dilated the arterioles. Administration of a vasodilator can then only increase the diameter of blood vessels in non ischemic vascular beds that are parallel to the ischemic ones. The result is coronary steal, a further reduction in the pressure downstream from the site of stenosis and further compromise of the blood flow to the ischemic region. When vasodilator therapy relieves angina, the favourable result is more likely to be attributable to the vasodilatation of the non coronary systemic vessels, which reduces peripheral resistance, thereby reducing the after load during systole and thus the work of the heart.[14]

CORONARY ARTERY DISEASE:

Coronary Artery Disease is due to the pathological changes in the arteries which causes insufficient coronary blood flow[15,16]. Death occurs suddenly due to the acute occlusion of the coronary artery or fibrillation of the heart, while some casualty happens due to the progressive weakening of the heart pumping, gradually around the time of weeks to years.[15] CAD can cause myocardial ischemia by three mechanisms:

(1) profound vascular spasm,

(2) formation of atherosclerotic plaques, and

(3) thromboembolism.

Vascular spasm is an atypical spastic condition, in which transiently contracts the coronary vessels. Vascular spasms are connected along with the earlier phases of CAD and are most often instigate by exposing to cold climate, physical effort or anxiety. Commonly, this state is reversible, which do not last long in order to damage the cardiac muscle. When only very less oxygen is obtainable in the coronary vessels, the endothelium discharges platelet-activating factor (PAF). PAF, which exerts a variety of actions, was named for its first discovered effect, activating platelets. Among its other effects, endothelium releases PAF, which diffuses into the vascular smooth muscle and by making it to contract and bringing the vascular spasm.[16]

Atherosclerosis is a degenerative and gradually developing arterial pathology, which directs to the occlusion of distressed vessels, which decreases vascular supply by them. Atherosclerosis is categorised by plaques, which is formed

beneath the vessel lining within walls of the artery. An atherosclerotic plaque has a lipid rich core enclosed by an unusual overgrowth of smooth muscle cells, which is covered by a collagen rich connective tissue cap. It projects into the vessel lumen, as the plaque emerges. These are the following complex sequence of events in the gradual **Development of Atherosclerosis**:

1. Atherosclerosis commences with the blood vessel wall damage that triggers an inflammatory reaction, which sets the point for plaque accumulation. Normally, inflammation is a defensive reaction, in which battle infection and encourages patch up of damaged tissue. However, persistent and low-grade inflammatory reaction over a course of decades, can insidiously head on to arterial plaque development and then lead on to the heart disease, if the source of the damage stays inside the vessel wall. Plaque formation likely has many causes. Suspected artery-abusing agents that has vascular inflammatory reaction includes free radicals, oxidised LDL cholesterol, elevated blood pressure, homocysteine, chemicals discharged from fat cells or even bacteria and viruses that damages the vessel walls. Oxidised LDL cholesterol considered to be the most common causative factor for Atherosclerosis.

2. Initially atherosclerosis is characterized by the deposition of excessive quantity of low-density lipoprotein cholesterol under the endothelium, that is moreover suspected as bad cholesterol, in combination with a protein carrier. Since LDL deposits inside the vessel wall, this cholesterol product turns into oxidized, mainly by oxidative wastes which are free radicals produced by the blood vessel cells.

3. Due to the occurence of oxidized LDL, it reacts on the endothelial cells to generate the chemicals,which draws monocytes to the injured site. These immune cells activates the local inflammatory response.

4. When they comes out of the blood and goes into the blood vessel wall, monocytes remains there permanently and transform into vast phagocytic cells known as macrophages. Macrophages voraciously phagocytise the oxidized LDL, till all these cells develop into crowded with fatty droplets which looks foamy over the microscope. These foam cells, which engorges the macrophages, deposit under the vessel lining which develops into a obvious fatty streak, the commencement of an atherosclerotic plaque.

5. The most primitive stage of a plaque is deposition of a cholesterol rich residue under the endothelium. Further, the disease advances as smooth muscle cells inside the vessel wall, which migrates on topmost site of the lipid growth from the muscular layer of the blood vessel which is just beneath the endothelium. This migration is activated by chemicals emitted from the inflammatory site. From their recent location, the smooth muscle cells carry on to break up and extend, inducing atheromas, which are the benign tumours of the smooth muscle cells inside the blood vessel walls. Maturing plaque is formed all together from the lipid rich residue and overlying smooth muscle.

6. When it continues to advance, the plaque gradually protrudes into the lumen of the blood vessel. The protruding plaque tapers the cavity from which the blood flows.

7. Oxidized LDL obstructs the release of nitric oxide from the endothelial cells, which further contribute to the narrowing of blood vessel. Nitric oxide is a local

chemical messenger, which relaxes the underlying layer of normal smooth muscle cells inside the blood vessel wall. Relaxation of these smooth muscle cells helps to dilate the blood vessel. Due to the reduction in the nitric oxide release, vessels which are injured by developing plaques, cannot dilate normally.

8. A condensing plaque also get involves with the nutrient replacement for cells positioned inside the arterial wall, which leads on to wall erosion around the areas of the plaque. The damaged area is encroached by fibroblasts, and forms a collagen rich connective tissue cap above the plaque. Sclerosis is the extreme progression of fibrous connective tissue, therefore it is called as atherosclerosis, which is characterized by atheromas and sclerosis along with odd lipid deposition.

9. In the later periods of the disease, Ca2+ frequently deposits in the plaque. The blood vessel so badly affected develop into hard and cannot distend easily.[16]

A most common location for the growth of atherosclerotic plaques is the initial few centimetres of the two major coronary arteries.[15]

COMPLICATIONS OF ATHEROSCLEROSIS

Atherosclerosis damages the arteries all over the body, however the crucial concerns include the impairment of the brain and heart vessels. Atherosclerosis is the most important reason for developing stroke, while it causes the myocardial ischemia in the heart. The following are the capable complications of coronary atherosclerosis:

■ **Angina pectoris:**

Gradual swelling of projecting plaque carry on to taper the vessel lumen and gradually reduces coronary blood flow, which urges frequent increasing spells of

brief myocardial ischemia, which is the capacity to correspond blood flow with cardiac oxygen requirement becomes very restricted. Even though the heart is not normally “felt”, pain is related to the myocardial ischemia. Such cardiac pain is called as **angina pectoris**, which is felt under the sternum, which also radiates to the left shoulder and along the left arm. The symptoms of the angina pectoris recur whenever there is an increase in the cardiac oxygen demand because of the coronary blood flow. For instance, heavy exertion or emotional stress. The ischemia linked with the typically transient angina strike, which is mostly interim and also reversible, which is reduced by rest, vasodilator drugs such as nitro-glycerine.[16]

THROMBOEMBOLISM:

The enlarging atherosclerotic plaque can break through the damaged endothelial coating , exposing blood to the underlying collagen of the plaque. Foam cells discharges the chemicals that can loosen the fibrous cap of a plaque by breaking the connective tissue fibres. Plaques, which has thicker fibrous caps are considered stable because they do not rupture. However, plaques which has thinner fibrous caps are considered to be unstable, so they are most likely to rupture and trigger clot formation. Normally, blood platelets does not stick on to smooth, healthy vessel wall. But when platelets is brought in contact with collagen at injured vessel, they adhere to it and help to promote the blood clot formation. Moreover, foam cells produce a potent clot promoter. An atypical blood clot adhered to the blood vessel wall is called thrombus. The thrombus progressively enlarges, till it totally obstructs the vessel or the constant course of blood flowing on the thrombus makes it very loose. As it leads downstream, such a freely floating clot obstructs entirely a minor vessel. Thus,

atherosclerosis results in a slow or rapid blockage of a coronary vessel by means of thromboembolism.[16]

■ Myocardial Infarction:

Following the complete obstruction of a coronary vessel, the cardiac tissue aided by the vessel dies immediately from oxygen scarcity and infarction appears, if not the area is perfused from the collateral blood vessels. During a heart attack, the extent of the injured area relies on the extent of the choked blood vessel. When the obstruction is larger in the vessel, the area deprived of blood supply also becomes larger. When there is complete obstruction of any one of the main branches, concludes in wide spread myocardial injury. Left coronary artery blockage is mainly obliterating than the right, as it provides blood supply to 85% of the cardiac tissue.[16]

A heart attack has four possible consequences: instant casualty, gradual casualty from difficulties, entirely functional recovery and recovery with weakened function.[16]

FACTORS AFFECTING ATHEROSCLEROSIS: [16]

In spite of the solid association amongst cholesterol and heart disease, more than half of the cardiac patients have a normal lipid profile and no other well determined threat features.

Obviously, these cardiac patients have other features that are concerned in the advancement of Coronary Artery Disease. Further, these similar features contributes to develop the atherosclerosis in those people with poor cholesterol levels.

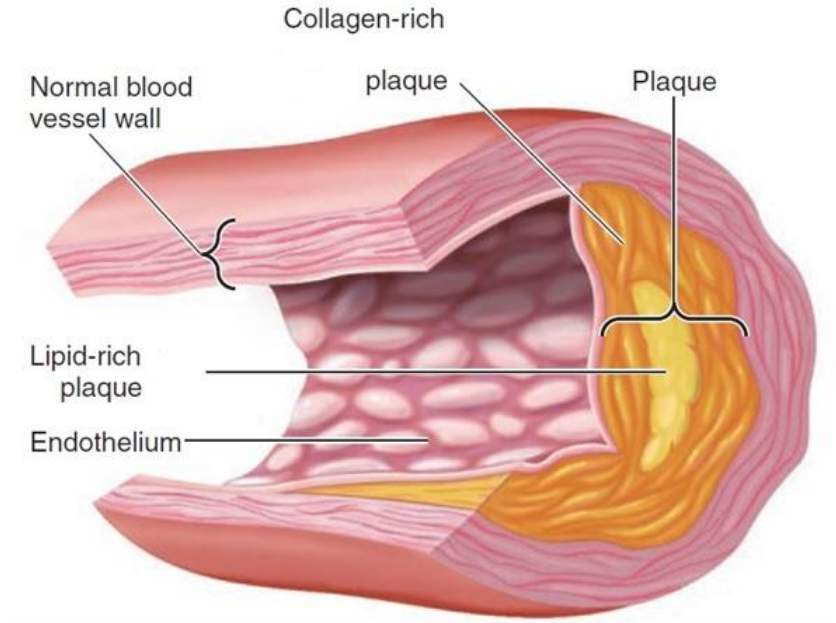


FIGURE 2 ATHEROSCLEROTIC PLAQUE FORMATION

The following are among the leading other possible risk factors:

■ Elevated blood concentration of the amino acid homocysteine was recently implicated as a strong predictor for heart disease. Homocysteine is composed as a transitional product during metabolism of the essential dietary amino acid methionine. Investigators believe homocysteine contributes to atherosclerosis by encouraging rapid growth of vascular smooth muscle cells, an early step in development of this artery clogging condition. Furthermore, homocysteine appears to break the endothelial cells causing oxidation of LDL, both of which can contribute to plaque formation. Three vitamin B, that is folic acid, vitamin B12, and vitamin B6, which all play key roles in pathways that clear homocysteine from the blood. Therefore, these B vitamins are all needed to keep blood homocysteine at safe levels.

■ Elevated levels of C-reactive protein, which is a blood borne indicator for inflammation, is having increased threat to develop coronary artery disease. People

who have higher level of C-reactive protein in their blood were three times more suspected to have a heart attack. As inflammation does a vital task in the progression of atherosclerosis, anti-inflammatory drugs like aspirin, aids in preventing the heart attacks. Moreover, aspirin guards against infarction throughout its function in preventing clot formation.

■ An infectious agent may be the underlying culprit in a significant number of cases of atherosclerotic disease. Among the leading suspects are respiratory infection-causing Chlamydia pneumonia, herpes virus, and gum-disease-causing bacteria.[16]

CONVENTIONAL ATHEROSCLEROTIC RISK FACTORS:[13]

- Smoking
    - Enhances the oxidation of LDL
    - Dysfunctional endothelial Nitric Oxide Biosynthesis
    - Increases C- Reactive Protein, Homocysteine.
    - Increases Soluble Intercellular Adhesion Molecule-1, Fibrinogen,.
    - Increases monocyte adhesion to endothelial cells, leads to spontaneous Platelet Aggregation.
- Hypertension
    - Systolic Pressure and Pulse Pressure have greater importance than Diastolic Blood Pressure in Cardiovascular Disease.
    - Systolic Pressure reflects the reduced arterial Elasticity. Pulse Pressure generally reflects Vascular wall stiffness.

- Low Density Lipoprotein Cholesterol

  - Involved in the Atherogenesis.

- High Density Lipoprotein Cholesterol

  - Augments Peripheral catabolism of Cholesterol by Ferrying Cholesterol from the vessel wall.

  - Transport Antioxidant enzymes which plays an important role in decreasing the quantity of oxidised Phospholipids in Atheromatic lesions.

- Triglyceride

  - Exposure of the Arterial wall to triglyceride possibly will encourage Atherosclerosis.

- Metabolic Syndrome, Insulin Resistance and Diabetes:

  - Accumulation of progressive glycation end products associated with Vascular Damage, causing impaired Endothelial and Smooth muscle function.

  - Augments Leukocyte bond to Vascular endothelium, which also impairs Nitric Oxide mediated Vasodilatation, a critical early step in Atherogenesis.

- Physical Exercise (No Pain, No Gain)

  - Reduces the Myocardial Oxygen demand and increases exercise capacity which correlates with lower levels of Coronary risks.

  - Reduces Adiposity, Diabetes Incidence, Decreases Blood Pressure.

- Improves Dyslipidemia and Vascular Inflammation.

- Obesity

- Defined as Body Mass Index of 30 or Higher.

- Impact on Vascular risk which is mediated by the interrelations along with the Glucose intolerance, Insulin resistance, Hypertension, Physical passivity and Dyslipidemia.

- Mental Stress

- Augments the Myocardial Oxygen requirements and also causes Coronary Vasoconstriction. Further linked to Platelet and Endothelial Dysfunction, Metabolic syndrome and initiation of Ventricular Arrhythmias.

- Depression

- Increases the Platelet Activation, Elevates the levels of high sensitivity C-Reactive Protein, decreases the Heart Rate.

NOVEL ATHEROSCLEROTIC RISK FACTORS:[13]

- High Sensitivity C-Reactive Protein,
- Serum Amyloid A,
- Homocysteine,
- Fibrinogen,
- Tissue Plasminogen Activator (tPA)
- Lipoprotein (a),

- D- Dimer,
- Apo lipoprotein B
- Plasminogen Activator Inhibitor 1 (PAI-1)
- Interleukin 6
- Soluble Intercellular Adhesion Molecule-1(sICAM-1)

Other Inflammatory biomarkers like Myeloperoxidase, Soluble CD 40 ligand and Metalloproteinase are under study as markers of underlying atherosclerosis.

DIAGNOSIS OF CORONARY ARTERY DISEASE:[13]

- Biochemical tests - Fasting Blood Glucose level, serum Creatinine, Total Cholesterol, Triglyceride, Low Density Lipoprotein Cholesterol, High Lipoprotein Cholesterol, Lipoprotein (a), and Inflammatory biomarkers.
- Cardiac biomarkers Troponin (T or I; cTnT or cTnI) and Creatine Kinase MB isoenzyme (CK-MB)
- Echocardiography
- Stress test
  - Exercise Electrocardiogram
  - Exercise - Single Photon Emission Computed Tomography(SPECT).
  - Adenosine Single Photon Emission Computed Tomography(Nuclear Stress Test)
  - Exercise Echocardiography.

- Dobutamine Echocardiography.

- Cardiac Magnetic Resonance Imaging (CMR)

- Projects efficient recovery subsequently after Percutaneous or Surgical revascularisation.

- Coronary Angiography

- American College Cardiology / American Heart Association guidelines to proceed to Coronary Angiography should be based on symptomatic status and risk stratification formed on clinical information and non-invasive investigation outcome.

- Invasive Technique for the Definitive diagnosis of Coronary Artery Disease and precise assessment of its anatomical severity.

- Newer Invasive Techniques like Intravascular UltraSonography (IVUS) gives a cross sectional analysis of the coronary artery and have substantially enhanced the recognition and evaluation of coronary atherosclerosis. And also the capability to distinguish the susceptibility of Coronary Atheroma.

- Studies incorporating both Coronary Angiography and Intravascular UltraSonography have demonstrated that the severity of Coronary Artery Disease may be underestimated by doing Angiography alone.

- CT Coronary Angiography is also evolving as a non invasive tool as well.

TREATMENT:[13]

American College Cardiology / American Heart Association guidelines for the initial medical therapy includes:

A = Aspirin and Antianginal

B = Beta Blocker and Blood Pressure

C = Cholesterol and Cigarette Cessation.

D = Diet and Diabetes

E = Exercise and Education

MEDICAL MANAGEMENT:

- Healthy Diet

- Reduction of Coronary risk factors such as smoking cessation, Exercise.

- Hormone replacement like Estrogens to menopause women and Testosterone to Andropause men.

- Treatment for Associated Diseases like Hypertension, Diabetes, Dyslipidemia

- Pharmacotherapy for secondary management which includes Aspirin, Clopidogrel, Beta Blockers, Angiotensin Converting Enzyme Inhibitors, Antioxidants.

PHARMACOLOGICAL MANAGEMENT:

- Nitrates - Nitro-glycerine, Isosorbide Dinitrate, Isosorbide 5- Mononitrate.
- Beta- Adrenoceptor Blocking agents- Atenolol, Metoprolol, Bisoprolol, Propranolol, Labetalol, Carvedilol
- Calcium Antagonists - Nifedipine, Verapamil, Diltiazem, Amlodipine, Felodipine, Nicardipine
- Ranolazine - Piperazine derivative Antianginal drug.
- Nicorandil - Nicotinamide ester which possesses nitrate moiety.
- Ivabradine - Specific and selective inhibitor of Funny current (I_f) ion channel
- Fasudil - Orally Available inhibitor of rho kinase.

OTHER THERAPIES:

- ❖ Spinal cord stimulation - Indicated for refractory angina cases who are unfit to do revascularisation by using a improved electrode into the epidural space.
- ❖ Enhance External Counter Pulsation - One of the optional treatment for Refractory Angina.
- ❖ Chelation : No benefit in the treatment of Coronary Artery Disease.

PERCUTANEOUS CORONARY INTERVENTION:

- Percutaneous Transluminal Coronary Angioplasty, Stenting and related techniques represents an important therapeutic option in the management of Coronary Artery Disease.

CORONARY ARTERY BYPASS SURGERY:

- Portal access Coronary Artery Bypass Surgery is performed using limited incisions with femoral-femoral Cardiopulmonary Bypass and induced cardiac arrest.
- Totally Endoscopic Enabled Coronary Artery Bypass Surgery to be done on the arrested heart.
- Off pump Coronary Artery Bypass Surgery is done using a standard median sternotomy with generally small skin incisions and stabilisation devices to reduce the motion of the target vessels while anastomoses are performed without Cardiopulmonary Bypass.
- Minimally Invasive Direct Coronary Artery Bypass is operated through a left anterior thoracotomy without Cardiopulmonary Bypass.[13,17]

TESTOSTERONE:

Testosterone is the chief hormone of the testes. It is a vital hormone for the male reproduction. Primarily, it enables the growth of male reproductive organs in fetal life, controls spermatogenesis, guides development of secondary sexual characteristics and also maintains male vigour.[5,15,18]

SOURCE:

Testosterone is synthesized mainly by the Leydig cells and also secreted from adrenal cortex, Ovaries and Placenta. Small amount of testosterone is secreted in the female also.[5,15,18]

STRUCTURE:

Testosterone is a C_{19} steroid with an –OH group at 17^{th} position. It is synthesized from cholesterol in the Leydig cells of the testis. It is also formed from androstenedione secreted by the adrenal cortex. Even though the biosynthetic pathways in all endocrine tissues that materialise steroid hormones are alike, the tissues differs only in the enzyme systems involved in the process. In the Leydig cells, 17 α-hydroxylase is present and in the adrenal cortex, 11- and 21-β hydroxylases are found.[5,15,18]

Pregnenolone is converted to Testosterone by two pathways: δ4 and δ5 pathways. Pregnenolone is therefore hydroxylated in the 17th position in the testis and then subjected to side chain cleavage to form dehydroepiandrosterone. Androstenedione is produced via progesterone and 17-hydroxyprogesterone as well. Dehydroepiandrosterone and androstenedione are then converted to testosterone.[5,18]

The secretion of testosterone is under the control of Luteinizing Hormone(LH), and the mechanism of stimulation of Leydig cells by LH involves increased formation of cAMP via the G protein-coupled LH receptor and Gs. cAMP increases the formation of cholesterol from cholesterol esters and the conversion of cholesterol to pregnenolone through the activation of protein kinase A.[5,15,18]

SECRETION

The testosterone secretion rate is 4 to 10 mg day. in normal adult males. The normal plasma concentration of testosterone is 300-1000 ng/dL in adult males and 30-70 ng/dL in adult females. It declines with the age in males.[5,18]

TRANSPORT & METABOLISM

98% of the testosterone in plasma is bound to protein off which 65% is bound to a β -globulin called gonadal steroid binding globulin (GBG) or sex steroid-binding globulin which also binds estradiol and 33% is bound to albumin. Only 2% of testosterone is free in plasma. The free testosterone enters the target tissues in which it is converted to its active form DiHydrotestosterone by 5 α Reductase. A small amount of circulating testosterone is converted to estradiol by aromatase, but most of the testosterone is converted to 17-ketosteroids by 17 β dehydrogenase. The principal ketosteroids are androsterone and its isomer etiocholanolone which are excreted in the urine. About two thirds of the urinary 17-ketosteroids are of adrenal origin, and one third are of testicular origin.[5,18,19]

While most of the 17- ketosteroids are weak androgens, it is important to indicate that not all 17-ketosteroids are androgens and not all androgens are 17-ketosteroids. Etiocholanolone has no androgenic activity, and intrinsically testosterone is not a 17-ketosteroid.[5,18,19]

ACTIONS

Adding up to their actions in the course of development, testosterone and other androgens has an inhibitory feedback effect on pituitary LH secretion, which develop and maintain the male secondary sex characteristics. It also has an important protein-anabolic and growth-promoting effect and along with FSH, maintain spermatogenesis.[5,18]

SECONDARY SEX CHARACTERISTICS

At puberty, boys develop extensive changes in hair distribution, body configuration, and genital size are the male secondary sex characteristics. The prostate and seminal vesicles expand, and the seminal vesicles begin to emit fructose. This sugar appears to act as the chief nutritional source for the spermatozoa. The psychic property of testosterone are hard to define in humans, however in trial animals, androgens trigger animated and aggressive behaviour. It has effects on sexual behaviour also. Even though body hair increases by androgens, scalp hair is decreased. Hereditary baldness often fails to develop if not dihydrotestosterone is present. [5,18,19]

ANABOLIC EFFECTS

Androgens increases the synthesis and decreases the breakdown of protein, which leads to an increase in the degree of growth. It claims that they cause the epiphyses to fuse to the long bones, hence eventually stopping growth, but it now appears that epiphysial closure is due to estrogens. Consequently to their anabolic properties, androgens affects moderate Na^+, K^+, H_2O, Ca^{2+}, SO_4^{-}, and PO_4^{-} retention. It also increases the size of the kidneys. [5,15,19]

MECHANISM OF ACTION

Testosterone binds to an intracellular receptor and the receptor - steroid complex, which binds to DNA in the nucleus, facilitating transcription of several genes. Furthermore, testosterone get transformed into dihydrotestosterone (DHT) by 5 α - reductase in some target cells and DHT binds to the similar

intracellular receptor being testosterone. Moreover DHT circulates, with a plasma level which is about 10% of the testosterone concentration. Testosterone–receptor network are less constant than DHT–receptor complexes in target cells. Hence, DHT formation is a method of augmenting the effect of testosterone in target tissues. There are two 5 α - reductases, encoded by different genes. Type 1 5 α -reductase is present in skin all over the body and is the forceful enzyme in the scalp. Type 2 5 α - reductase is present in genital skin, the prostate, and other genital tissues. Testosterone–receptor complexes are important for the maturation of wolffian duct structures and subsequently for the growth of male internal genitalia, however DHT–receptor network are vital for the development of male external genitalia. Besides, DHT–receptor complexes are mainly responsible for bulging of the prostate and most likely of the penis at the time of puberty, also for the facial hair, acne and the temporal recession of the hairline. Conversely, the increase in muscle mass and the growth of male sex drive and libido rely mainly on testosterone rather than DHT.[5,19]

TESTICULAR PRODUCTION OF ESTROGENS

Above 80% of the estradiol and 95% of the estrone in the plasma of adult men is formed through extragonadal and also extra adrenal aromatization from circulating testosterone and androstenedione. The rest comes from the testes. Little estradiol in testicular venous blood comes from the Leydig cells, although some is furthermore produced as result of aromatization of androgens within Sertoli cells. In men, the plasma estradiol level is 20 to 50 pg/mL and the total production rate is approximately 50 μg/ d. In contrary to the condition in women, estrogens production moderately increases with aging men.[5,19]

CONTROL OF TESTICULAR FUNCTION

FSH is tropic for Sertoli cells. FSH and androgens preserve the gametogenic function of the testes. In addition, FSH activates the discharge of Androgen Binding Protein (ABP) and Inhibin. Inhibin gives feedback to inhibit FSH secretion. LH is tropic for Leydig cells and stimulates the secretion of testosterone, which consecutively gives feedback to inhibit LH secretion. Hypothalamic lesions produce atrophy of the testes and failure of their function.[5,19]

INHIBINS

Testosterone decreases the plasma LH, but only in large doses and it has no effect on plasma FSH. In patients with the atrophy of the seminiferous tubules, Plasma FSH is increased, but levels of testosterone and LH secretion are normal. These explanation has taken to the search for inhibin, a factor of testicular origin which inhibits FSH secretion. There are two inhibins in extracts of testes in men and in antral fluid from ovarian follicles in women. They are formed from three polypeptide subunits: a glycosylated α subunit and two nonglycosylated β subunits, β_A and β_B. The subunits are formed from precursor proteins. The α subunit combines with β_A to form a heterodimer and with β_B to form an additional heterodimer, along with the subunits connected by disulfide bonds. Both α β_A (inhibin A) and α β_B (inhibin B) inhibit FSH secretion by a direct action on the pituitary, although it now appears that it is inhibin B that is the FSH-regulating inhibin. Inhibins are produced by Sertoli cells in males and granulosa cells in females.[5,19]

The heterodimer β_A β_B and the homodimers β_A β_A and β_B β_B are also formed. They stimulate rather than inhibit FSH secretion and consequently are called activins. Their function in reproduction is unresolved. However, the inhibins and activins are units of the TGF β super family of dimeric development factors that also includes MIS. Activin receptors have been identified and belong to the serine/threonine kinase receptor family. Inhibins and activins are found not only in the gonads but also in the brain and other tissues. Within the bone marrow, activins are involved in the development of white blood cells. In embryonic life, activins are concerned with the formation of mesoderm.[5,19]

In plasma, α 2-macroglobulin binds activins and inhibins. In tissues, activins bind to a family of four glycoprotein called follistatins. Binding of the activins inactivates their physiologic function remain unresolved.[5,19]

GONADOTROPIN-RELEASING HORMONE:

A major share of the control of sexual activities in both the male and the female starts through secretion of Gonadotropin-releasing hormone (GnRH) by the hypothalamus. This hormone sequentially triggers the anterior pituitary gland to emit two other hormones, which are called as Gonadotropic hormones: (1) luteinizing hormone (LH) (2) follicle-stimulating hormone (FSH). In turn, LH is the primary trigger for the secretion of testosterone by the testes, and FSH mainly stimulates spermatogenesis.[5,19]

EFFECT OF GNRH

Arcuate nuclei of the Hypothalamus secretes GnRH, which is a 10-amino acid peptide. All these neuronal endings terminate predominantly in the median eminence of the hypothalamus, where they emit GnRH advancing into the Hypothalamic-Hypophysial portal vascular system. Then the GnRH in the hypophysial portal blood, is passed to the anterior pituitary gland, and that promotes the discharge of the two gonadotropins, LH and FSH. GnRH is secreted once every 1 to 3 hours periodically a few minutes at a time. The strength of this hormone's spur is influenced in two ways: (1) by the frequency of these cycles of emission and (2) by the quantity of GnRH released with each cycle.[5,15,18]

The anterior pituitary gland which is secreted by LH, occurs in cycles with LH following fairly the pulsatile secretion of GnRH. On the contrary, FSH secretion increases and decreases only vaguely with each fluctuation of GnRH secretion, rather it changes more leisurely over a phase of many hours in reaction to longer-span variation in GnRH. Because of the much intense association between GnRH secretion and LH secretion, GnRH is moreover broadly identified as LH-releasing hormone. [5,15,18]

GONADOTROPIC HORMONES: LH AND FSH

LH and FSH, are secreted by the same cells, which is called as called gonadotropes, in the anterior pituitary gland. In the deficiency of GnRH release from the hypothalamus, the gonadotropes in the pituitary gland secrete virtually no LH or FSH. Both LH and FSH are glycoproteins. They apply their effects on their target

tissues in the testes primarily by initiating the cyclic AMP second messenger system, which in turn activates specific enzyme systems in the respective target cells.[15]

STEROID FEEDBACK

The functions of the testes are regulated by steroids, which is the current "Working Hypothesis". There is a increase in the pituitary matter and secretion of FSH and LH after Castration and hypothalamic lesions inhibit this rise. Testosterone inhibits LH secretion by acting directly at the anterior pituitary and also through the impediment of the GnRH discharge from the hypothalamus. Inhibin inhibits the FSH secretion by acting directly on the anterior pituitary.[5,18]

Reacting to LH, some of the testosterone conceded from the Leydig cells soaks the seminiferous epithelium and ensures the Sertoli cells to receive the peak local concentration of androgen, which is necessary for natural spermatogenesis. Systemically managed testosterone does not increase the androgen concentration in the testes to a great degree, and it inhibits LH secretion. Accordingly, the net effect of systemically administered testosterone is generally a decrease in sperm count. Thus, Testosterone therapy has been recommended as a means of contraception for Males. However, the dosage of testosterone required to suppress spermatogenesis produces sodium and water retention. The likely use of inhibins as male contraceptives is now being opened up.[5,18]

TESTOSTERONE DECLINE WITH AGE:

Vermeulen et al, Rubens et al, Baker et al, Pirke et al, Purifoy et al, Bremner et al, Tenover et al, Gray et al, Ferrini et al, Harman et al have illustrated a drop in androgen levels with advancing age.[20-29] However, contradicting females, males do not encounter the highly distinguished, abrupt and sudden drop in sex hormone concentration and termination of reproductive ability as their age increases. Contradicting the menopause, the 'andropause' usually brings in quite vague clinical features, which includes decreased sex drive, fatigue, dryness of the skin, depression and deprived attention, features which are frequently considered merely as a usual ingredient of the progression of age. Symptoms consists of crumpled dry skin with pale outline, receding hairline, muscular atrophy and gynaecomastia. Generally Hypogonadism is not diagnosed and not treated, because of the unclear characteristics of the symptoms. It is identified in some patients but it is not treated owing to a alleged fear concerning harmful iatrogenic consequences on the Heart and Prostrate. The natural and impending causes concerned with the drop in testosterone concentration with the aging was studied by **Harman et al**[29]. He established that both total and free testosterone declined at a steady pace from the third to ninth decade in 890 normally healthy men,. As the age increases, the decline in free testosterone concentration was notable because of the substantial increase of sex hormone binding globulin. All these explanations were not related to obesity, co morbid conditions, smoking, medication and ethanol abuse.[5,15,19]

TESTOSTERONE LEVEL AND CORONARY ARTERY RISK FEATURES:

In the past, it was understood that the elevated incidence rate of coronary artery disease in men, possibly described by variation in risk factor studies between genders. Generally, Men shows behaviour which are considered more harmful for the heart by the elevated quantity of smoking and by foods which are more loaded with saturated fats.[30] In spite of this, it has been revealed that variation in behavioural profiles of men do not report for the extra load on Coronary Artery Disease, which was explained by **Njolstad et al** and **Raynor et al**[30,31].

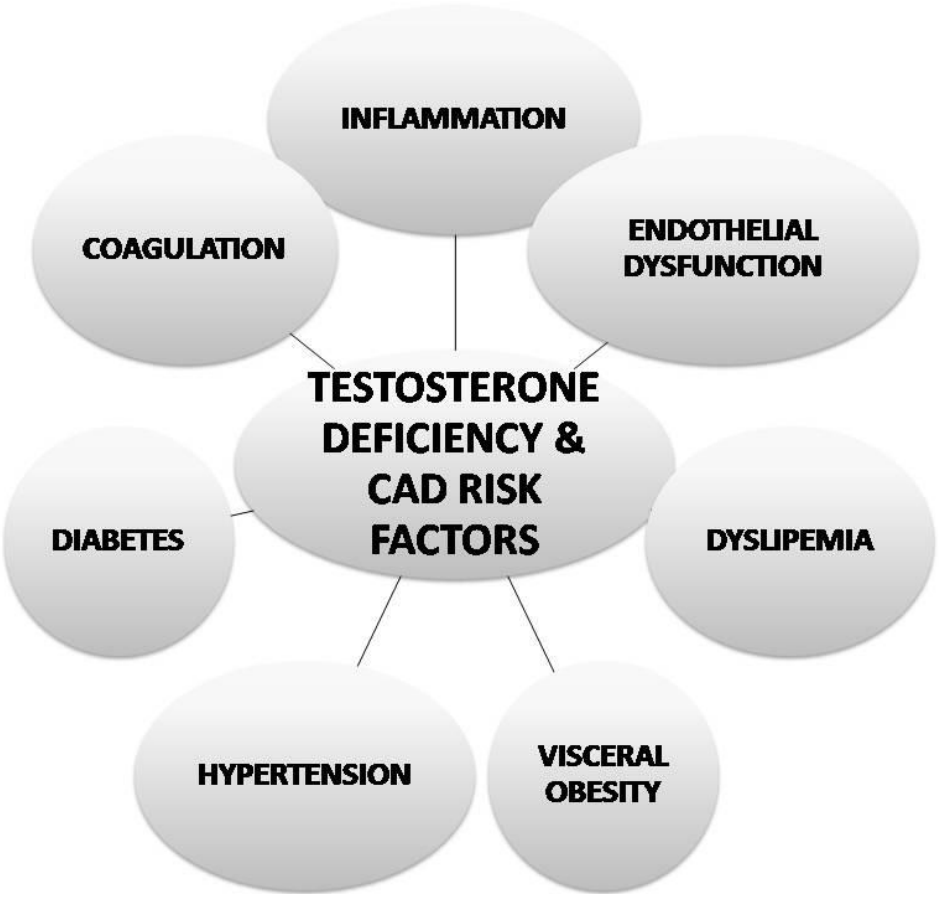


FIGURE 3

The development and progression of Coronary Atherosclerosis and testosterone deficiency are greatly impacted by the interrelation of numerous risk features as shown in Figure 3.

VISCERAL OBESITY

Increased prevalence rate of Testosterone Deficiency with visceral obesity and related disorders is seen in men. The hypogonadal - obesity - adipocytokine cycle produces a state where testosterone is rapidly metabolized and the hypothalamic-pituitary axis is impaired and unable to respond and hence replenish testosterone levels.[32]

GLUCOSE INTOLERANCE AND DIABETES

Diabetes and the metabolic syndrome are major cardiovascular risk factors. Testosterone deficiency has a higher prevalence in these conditions and is associated with insulin resistance. [32]

DYSLIPIDEMIA

Testosterone deficiency is related with the changes in the Cholesterol level, as they are consistent with a pro-atherogenic background. **Barrett-Connor et al[33], Haffner et al[34], Simon et al[35], Dai et al[36], Heller et al[37]** and **Hromadova et al[38]** have found that testosterone has a negative correlation along with Total Cholesterol, Low-Density Lipoprotein (LDL) and Triglycerides. Healthy and diabetic men have a significant positive association relating testosterone and HDL cholesterol levels. In healthy young men where hypogonadism was chemically induced, testosterone replacement therapy produced a rise in Total Cholesterol and LDL cholesterol and a drop in HDL cholesterol. **Whitsel et al[39],** a meta analysis of several studies has demonstrated that testosterone replacement produces a reduction in total and LDL cholesterol and a small decrease in HDL cholesterol.[32]

COAGULATION

Testosterone deficiency is associated with a pro-coaguable state. Major clotting factors, that have been shown to be linked to testosterone levels are plasminogen-activator inhibitor type one (PAH), fibrinogen and tissue plasminogen activator (tPA). Within many cross-sectional analysis, low testosterone levels are related together with elevated fibrinogen concentrations.[32]

Factor VII, which is concerned in the transformation of prothrombin to thrombin, associates inversely with testosterone. Myocardial infarction is associated with a fall in tPA and rise in PAH levels. These changes are accompanied by a fall in testosterone.[32]

One of the complications of testosterone treatment is a raised haematocrit caused by raised erythropoiesis. Polycythaemia is related with hyper viscosity and therefore an increased risk of thrombosis. Monitoring of the haematocrit is essential to the management of testosterone therapy and the dose can be lowered to reduce these changes, A slight elevation of the haematocrit is unlikely to be associated with an increased risk however, each patient and their co-morbid state needs to be assessed on an individual basis. In recent years there have been unease concerning the augmented threat of thromboembolism by hormone substitution therapy in women. The evidence in men suggests that this is not the case with testosterone replacement therapy and indeed there may be a beneficial effect in hypogonadal subjects.[32]

HYPERTENSION

Men with hypertension have lower testosterone levels than men with normal blood pressure. Potentially, testosterone may lower blood pressure with the reduction peripheral vascular resistance. There also may be an effect of testosterone on activation of the renin-angiotensin system.[32]

ENDOTHELIAL DYSFUNCTION

The data on the effects of testosterone on endothelial dysfunction estimated on the brachial artery through flow-mediated vasodilatation are conflicting. Further research in this area is necessary to clarify that whether Testosterone has favourable or adverse outcome on endothelial dysfunction.[32]

TESTOSTERONE AND INFLAMMATION

Atherosclerosis is intimately linked with a pro-inflammatory milieu. A local inflammatory response is integral to the early stages of the pathogenesis and is also involved in the instability of the established plaque. Inflammatory proteins which consist of C-reactive protein, Fibrinogen, Interleukin can be raised in the circulation of people with atherosclerosis. Little is known regarding the role of testosterone on the immune system. Testosterone substitution to treat hypogonadism has resulted in an improvement in the systemic lupus erythematosus.[32]

TESTOSTERONE AND ANGINA

Testosterone was first used to treat the Angina in both Males and Females in the early 1940s. **Jaffe et al[40]**, a placebo-controlled study in 1977 found that

testosterone treatment in 50 males who had Coronary Heart Disease produced 32% decrease in the time towards 1 mm ST-segment inversion by stress treadmill testing after 1 month and 51% after 3 months. The study showed as the lesser the baseline bio available testosterone, better the favourable result of testosterone treatment on the time to ischemia. A further study involving men along with angina and explicit hypogonadisrn revealed that 1 month's treatment with testosterone led to a 74 seconds amelioration in the time towards 1 mm ST inversion.[32]

Acute testosterone administration directly into the coronary circulation at cardiac catheterization in humans leads to a rapid vasodilatation and an increase in coronary blood flow within 2-3 min of treatment. This effect is dose-dependent and occurs at testosterone concentrations within the normal physiological range. Furthermore an acute intravenous bolus of testosterone before going on to exercise stress testing shows in a substantial improvement in ischemia. The mechanism mediating the rapid onset of action is non-genomic and is likely to be through an action on calcium and potassium voltage-operated channels.[32]

TESTOSTERONE AS A VASODILATOR

The majority of studies using isolated blood vessels in vivo have shown that testosterone acts as a vasodilator. Effects of testosterone have been demonstrated in isolated human vessels comprising mesenteric and pulmonary arteries and more recently, gluteal arteries from subcutaneous skin. After 3 months of androgen suppression treatment for prostate cancer, vascular stiffness which was measured using pulse-wave analysis increased in the radial artery and the aorta.[32]

The vasodilatory effect is of rapid-onset, acting within 2-3 min of testosterone administration. The speed of action, and the findings that the outcome is not blocked by the means of flutamide. Flutamide is a classical androgen receptor blocker and persists in the mouse which is testicularly feminized, and also has an inactive androgen receptor which strongly suggests that it is not dependent of the typical androgen receptor. The effect is also independent of the endothelium nitric oxide and cyclo-oxygenase actions. Pharmacological concentrations are required in the isolated artery model to elicit the vasodilatory effect However, more recent studies on isolated vascular smooth muscle cells have illustrated straight inhibitory property on calcium channels at physiological concentrations. The exact mechanism by which testosterone mediates its vasodilatatory action may be either through activation of potassium channels or blocking calcium channels. Testosterone has been shown to activate calcium-sensitive potassium channels and to have a calcium antagonistic action. Electrophysiological and microfluorimetry studies in a vascular smooth muscle cell line have provided evidence that at physiological concentrations testosterone inhibits L-type voltage-gated calcium channels. The inhibitory effect of testosterone was also rapid in this system occurring within 2 min. This confirms that testosterone alone is blocking these channels and is not dependent on conversion to oestradiol. The L-type calcium channel consists of four protein subunits of which the main α1c subunit forms the pore. Human embryonic kidney cells transfect with the α1c subunit exhibited a similar inhibitory action. This implies that testosterone acts as a calcium channel blocker and has a similar action to commonly prescribed

calcium channel blocking agents, such as nifedipine and amlodipine usually used for the treatment of angina and hypertension.[32]

Testosterone therapy in males with Coronary Artery Disease has been revealed to enhance Flow-Mediated Brachial Artery Vasodilatation. It appears because of the consequence of nitric oxide discharge on the endothelium. Certain variations are evident in the short and longer term. Conversely, hypogonadal men who do not have cardiovascular disease have a higher surge and also nitrate-arbitrated brachial artery vasodilatation. Testosterone substitution leads to a restoration of brachial artery reactivity to normal. **Ong et al[41]** have shown conflicting effects of testosterone on brachial artery reactivity. For example, flow-mediated however not the nitrate-arbitrated brachial artery vasodilatation raises into the men, with prostate carcinoma treated with either chemical or surgical castration.[32]

ENDOGENOUS TESTOSTERONE IN MEN WITH CAD:

Generally, it is established that males live through a steady drop in their testosterone concentration as their age raises[23-26,28,29]. And male sex is believed to be a potent risk feature for developing Coronary Artery Disease. Concurrently, these two data have provoked several researchers to explore a probable correlation between testosterone and Coronary Artery Disease. In the past decade, the number of data with evidences which associates reduced testosterone concentration along with Coronary Artery Disease is progressively emerging.

Men with reduced amount of endogenous testosterone are further susceptible towards acquiring Coronary Artery Disease during their lifetimes which is recommended by the growing body of evidences.[42-47] Although, this is in straight disparity from previous studies results which was unsuccessful in obtaining any major Correlation among lower testosterone concentration and advancement of the Coronary Artery Disease.[33,48-50] There are two key potential complex factors that the earlier reports in general were unsuccessful to report. The sub fraction of testosterone utilized to execute the investigation and the approach worn to report in favour of subclinical Coronary Artery Disease are the key factors.

Usually in the serum of humans, testosterone survives in two diverse sub fractions. The biologically dormant structure of testosterone, which is firmly linked to SHBG. Hence, they are not capable of binding with the androgen receptors. [51,52] The bio available testosterone which is the biologically functional sub fraction of testosterone, is slackly linked towards albumin and liberally flows in the blood, which is also called as free testosterone.[51,52] The addition of all testosterone sub fractions is referred as Total testosterone. As a result, it is claimed to make use of the biologically functional type of testosterone in assessing the relation with the Coronary Artery Disease, should yield mostly the authentic outcomes. Although, we need further study to ultimately establish whether or not bio available testosterone outshines free testosterone like an indicator of hormone action. **English et al**[43] reported evenly for bio available testosterone level and subclinical Coronary Artery Disease and he established that statistically significant decreased concentration of both bio available and free testosterone in cases with

angiographically confirmed Coronary Artery Disease analogized along with control subjects who had normal coronary arteries. Later, the above said statement was authenticated by **Rosano et al**,[46] who proved that the individuals who were angiographically confirmed Coronary Artery Disease, had statistically significant lesser values of bio available testosterone.

These results were fixed by the four further studies. Even though we have to mark that nobody has explicated together for both bio available testosterone level and subclinical Coronary Artery Disease concurrently.[42,44,45,47] Conversely, negative relationship among testosterone values and the prevalence of Coronary Artery Disease was found by certain researchers. While **Kabakci et al**[49] conducted the study with total testosterone and free testosterone values to control for subclinical Coronary Artery Disease by evaluating Coronary Angiography outcome of both patients and controls. This constitutes the major restriction of this analysis, since the researchers could not completely assess for the biologically functional testosterone.

ENDOGENOUS TESTOSTERONE AND MORTALITY:

The above stated fall in testosterone in certain men has formerly been considered just as role of the biological ageing process. But the latest reports reveals that the reduced baseline testosterone concentration is the important prognostic indicator used to define mortality, even after managing the consequences of co-morbid states.

Hypotestosteronaemia was a indicator for mortality in 6-months time in a group of 44 aged hospitalised patients, which was reported by **Shores et al**[53]. The subsequent analysis showed the same set of people carried out the computer programmed study of Veteran's Affair's Medical record. Further, they analysed on 850 males for a 4 to 8 years time, managing for co-morbid states that would have influenced mortality like simultaneous cancer. Men with the lower level of testosterone had an 88% significant raise in all the source mortality threat, while matching up with normal testosterone concentration was also established.

The In CHIANTI report[54] showed that an age related decline in bio available testosterone was connected with enhanced risk of Mortality, in 2007. A six-year follow-up survey was done among 410 males who were aged above 65 years, and established the most distinct and statistically significant outcome, when lower testosterone level was related with relative drop in dehydroepiandrosterone sulphate and insulin-like growth factor. There is a disparity to men together with all the three hormones higher than the men with single, double or triple hormones in the least quartiles were augmenting on added chance for fatality.

Over a period of almost twenty years, **Laughlin et al**[55], in 2008, established a considerable drop in the level of bio available testosterone, however not the level of total testosterone with age, which was demonstrated on a group of 794 men with the average age of 71 years. The mortality risk was higher for the males in the least baseline quartile of the levels of total testosterone and bio available testosterone matched up together with those, who are in the highest quartile. Following the alteration of adiposity, age and lifestyle options, the mortality

risk was 44% more among the least and uppermost quartiles for the total testosterone level. 50% more among the minimum and maximum quartiles for the level of bio available testosterone in which Hazard Ratio was 1.50 and 95% Confidence Interval was 1.15–1.96.

The European Prospective research on Cancer Norfolk study[56], the major study analysing the outcomes of endogenous testosterone concentration and mortality, which prospectively examined the death in 11,606 fit males due to any reason and Cardiovascular Disease among the forty and seventy nine years age group during the follow up period. Around a six to ten years observational spell, they found that there was a statistically highly significant correlation among the level serum testosterone and mortality owing to all the causes which is 825 deaths, cardiovascular disease which is 369 deaths and cancer which is 304 deaths. P value was less than 0.01 for Cardiovascular mortality, which was statistically significant.

Malkin et al[57] analysed 930 males with angiographically verified Coronary Artery Disease were prospectively monitored for a 7 year phase and established that a baseline incidence of hypogonadism in this group to be 24%. The mortality rate was 21% in the group of androgen deficiency and in the eugonadal group, it was only 12%. Lower bio available testosterone concentration, even if not the level of total testosterone considerably impacted the all the cause and cardiovascular deaths following this analysis, which proposes that it is the most precise test in order to identify pathological defect and threat matched along with the former tests. Hence, lower level of testosterone seems to be a indicator for Mortality.

TESTOSTERONE AND CONGESTIVE CARDIAC FAILURE:

In the Western Countries, Coronary Artery Disease is the prime core source for cardiac failure. Still, precise association among testosterone and cardiac failure was not reported to the similar extent like association among Testosterone and Coronary Artery Disease. Cardiac failure is regarded as a catabolic condition by the initiation of maladaptive neurohormonal stimulation, inflammatory cytokines and vasodilator inability. Testosterone makes use of the outcome, which resists these alterations, as discussed earlier. In men with cardiac failure, Positive association of Cardiac output with the concentration of Serum Testosterone was revealed. Acute and intravenous management of testosterone intensively raised cardiac output in one of the analysis. [58]

Analysis was done on the outcomes of frequent use of testosterone supplementation. **Pugh et al**[58] showed developments following twelve weeks of testosterone therapy in men with Cardiac failure, in work out ability and in clinical symptoms in a small placebo controlled report. In another larger placebo-controlled report, showed alike outcomes which established with upgrading in work out ability, clinical symptoms, maximal strength, insulin resistance, reduction in Electrocardiographic Q-T interval and VO2 max.[57] Although these primitive trails are positive, further assessment is necessary to clarify the effects of testosterone therapy in the cardiac failure and the enduring outcomes of the Testosterone replenishment.

TESTOSTERONE TREATMENT IN CARDIOVASCULAR DISEASE:

Testosterone therapy is divided into two sets on the basis of facts concerning the cardiovascular outcomes. The consequences on cardiovascular risk factors, like Hypertension and Dyslipidemia, avails the straightforward clinical results of testosterone therapy on the heart itself and the benefit of an indirect consequence on Coronary Artery Disease.[32]

In men with type II diabetes, Testosterone replenishment has exposed to decrease Total cholesterol, LDL cholesterol and lipoprotein A, yet it was found on men who was previously on statin treatment. Testosterone therapy is connected with better lipid profiles with the drop in the total cholesterol and LDL cholesterol in the analysis of elderly and hypogonadal men.[59]

Arterial hardening and Hypertension are linked along with the Hypotestosteronaemia. There were numerous studies on eugonadal, hypogonadal and obese men of testosterone substitute therapy and stated that remarkable decline in the Systolic and Diastolic pressure during the spell of six months to ten years. Alike favourable outcomes of frequent testosterone treatment have revealed in a trail of testosterone treatment during the spell of twelve-month in decreasing Body Mass Index. In type II diabetic men, Testosterone therapy produces enhanced blood glucose control and augmented insulin sensitivity. And also it was found on the trails of testosterone therapy that most favourable alterations in the profiles of pro-inflammatory and anti-inflammatory cytokines. [59]

Rosano et al[46] demonstrated in a group of men who were just ready to carry out the stress treadmill testing and explored the acute outcomes of

testosterone treatment intravenously. Following the intravenous testosterone treatment, count to ischaemia was extensively extended, when it was matched up to baseline and placebo.

However, in the perspective of persistent testosterone treatment, **English et al**[60] revealed alike outcomes. In Coronary Artery Disease men, who were angiographically confirmed, were given twelve weeks of trans-dermal testosterone treatment and found that notably augmented count to ischaemia following the stress testing. Men with the least testosterone concentration had the maximum anti-ischaemic impression.

Malkin et al[57] executed a alike analysis of Testosterone Treatment which progressed the hypothesis, in the men with angina. However engaged men only with the substantial hypogonadism. The rise in count to ischaemia was more higher in the treadmill analysis. Additionally, there were considerable enhancements in clinical features and decrease in the pro inflammatory cytokine that is tumour-necrosis factor-A and favourable variations in Cholesterol levels. The anti-ischaemic consequences of testosterone treatment in an additional analysis, were established up to one year.

Saad et al[61] in a recent review paper, the beneficial outcomes on cardiovascular risk features, following testosterone treatment, which includes structure of the body, blood pressure, lipid panel and glucose level were illustrated. The favourable outcomes started to commence after three months of initiating testosterone therapy were demonstrated. Yet, progressing beneficial effect was witnessed till nine months in the task of enhancements of blood pressure, twelve

months in the task of better glucose regulation and till two years in the task of enhanced cholesterol levels.

In spite of previous unease on testosterone treatment in men with increasing age, currently we have great and promptly rising mass of data, which recommends that testosterone substitution in men who have cardiovascular disease is secure and efficient. Still, the outcome of testosterone replenishment treatment on the overall mortality and patient's benefit shall require some huge, potential and randomized studies. The subsequent large action is definitely the attractive part. Globally, millions of men are influenced by the Coronary Artery Disease and the incidence of hypogonadism were assessed on roughly one-quarter in this population. And the prize required to effectively substitute testosterone treatment in the affected men are potentially very huge. [61]

ADVERSE EFFECTS OF TESTOSTERONE THERAPY AMONG MEN:

In the past, there were two major worries about testosterone treatment among men. The first concern was that it may endorse Coronary Heart Disease. The other concern was that the testosterone replenishment treatment may induce prostate cancer. Optimistically, there were many recent studies which worked with the past concern and also produced guaranteed outcomes, concerning physiological amount of testosterone concentration and the men's heart. Supraphysiological quantity of testosterone replenishment treatment was utilised in an effort to enhance the muscle potency in a recent trail of fragile hypogonadal men. The pharmacological quantity of testosterone has considerably improved muscle

power, however the study was dropped much earlier due to an excessive cardiovascular consequences, was also further demonstrated. The authors further stated that twenty three patients taking testosterone therapy had cardiovascular problems and on this basis the study was discontinued.[62]

Furthermore, they had barely six genuine end points in the treatment group, in contrast to only one in the placebo group. Almost half of the group had a past record of having cardiovascular disease and the other half had substantial cardiovascular threat features. For exact substitution therapy, males with hypogonadism must be dealt alone with the physiological dosage of testosterone, was demonstrated by this study. It also described that testosterone substitution should be administered in the similar approach like that of thyroid hormone substitution. Replenishment doses must be intended to sustain normal physiological concentration. In the Basaria study[62], similar or poorer consequences might have been observed, if it was completed in hypothyroid patients along with more Coronary Artery Disease threat and also, if the substitution was directed at supra-physiological levels. The other upset was probably due to the data that prostate cancer has to be effectively managed by androgen suppressive treatment. But, epidemiological and clinical analysis have disappointed to establish any correlation among principal testosterone concentration and the probability of getting prostate cancer over the last decade. Likewise, no trials have proved that lesser than normal testosterone concentration are preventive versus getting prostate cancer.[63]

English et al[60] had given testosterone through trans-dermal route to the males who had established angina. During the trial period, they observed

the prostate-specific antigen concentration and there was no significant change seen. Moreover, testosterone concentration falls along with the increasing age, while the incidence of prostate carcinoma ascends. Testosterone treatment is obviously contra-indicated in males with prostate cancer and drop in the testosterone concentration are favourable. On the other hand, there is no indication from our data, favouring a contributory part of testosterone replacement concentration on the physiological normal range, along with the probability to progress into the prostate cancer. Actually, with the apparent data regarding decreased testosterone level and increased mortality, yet it is advised to withhold the testosterone suppressive treatment for the aged men who has localized prostate cancer because of decreased survival.[60,64]

ASSOCIATION BETWEEN TESTOSTERONE AND OBESITY:

The exact process of action of interrelation between testosterone and obesity was unidentified. The interrelation of testosterone and obesity might be an outcome of the enhancement of lipolysis by testosterone in the adipose tissue of abdomen. Furthermore, known that adipose tissue also had an increased accumulation of the aromatase enzyme,which might augment the adipose tissue and causing in further transformation of testosterone into estrogen, thus resulting hypogonadism. On the other hand, by rejecting the hypothalamus-pituitary-testicular axis, greater abdominal obesity may result in decreased testosterone discharge. Lastly, testosterone is the vital aspect, by stimulating the enzyme 11-hydroxysteroid dehydrogenase, it acts on the adipose tissues, by which glucocorticoids might have converted into their inactive form.[65]

Testosterone Deficiency are also seen in the patients who are suffering from chronic diseases like Chronic Kidney Disease, Human Immuno Deficiency Virus, Chronic Lung Illness, Diabetes Mellitus and various genetical forms like Klinefelter syndrome.[66,67] The other known sources for hypotestosteronemia are castration, Trauma, Radiotherapy or chemotherapy, any acute conditions and the tumours of Pituitary.[66,68] There is a mystery that whether lower level of testosterone in the sick patients, is the source for their sickness or it is the outcome of the disease. Reactive oxygen species (ROS) are produced by the Leydig cell's mitochondria, which are the standard derivative of testosterone synthesis. The deposit of ROS eventually may produce injury to the DNA of the Leydig cell, which makes it incompetent to produce testosterone.[69]

MATERIALS AND METHODS

This study was done at the Department of Physiology, Thanjavur Medical College, Thanjavur. The study group was from the General Community in and around Thanjavur. The ethical committee approval was obtained for this study. The study was case control type and conducted between October 2015 and May 2016. The patients were selected from those, who were admitted for diagnostic Coronary Angiography.

For this study, Serum Total Testosterone (ng/dL) level, FSH (mIU/ml) level and LH (mIU/ml) level were analyzed by ChemiLuminescence ImmunoAssay. Patients underwent thorough Clinical Examination and Overnight Fasting blood samples were taken from 40 male patients referred for diagnostic Coronary Angiography, as of symptoms indicative of Coronary Artery Disease and 40 Control Group of same age group and sex. The quantity of Coronary Artery Stenosis was >50%. The results of Angiogram was reported by the Cardiologist, before the Hormonal assay.

Inclusion criteria:

- Patients who were referred for Diagnostic Coronary Angiography.
- Degree of Coronary Artery Stenosis > 50%
- CRP(<5mg/l)

Exclusion criteria:

- Hypogonadism
- Hypopituitarism
- Taking drugs that might affect sex hormone level

- High CRP(>5mg/l)
- Previous Cardiovascular Event
- Coronary or Periphery Atherosclerosis.
- Degree of Coronary Artery Stenosis < 50%.

FIGURE 4

COBAS 6000 FOR CHEMILUMINESCENCE IMMUNOASSAY

FIGURE 5: BLOOD SAMPLES

Venous Blood samples were collected from the subjects, following an overnight fasting, so as to determine the serum and were sent to Bioline Laboratory. Serum levels of Testosterone, FSH and LH were calculated using ChemiLuminescence ImmunoAssay by Cobas 6000. Patient's hormone level were matched with the healthy control group.

Coronary Angiography was done to establish the incidence of Coronary Artery Stenosis. The Coronary Angiography was performed by a skilled Interventional Cardiologist in the catheterization laboratory and the outcome was reported by an Expert Cardiologist. Significant coronary stenosis and Coronary Artery Disease were defined, if there was 50% or more restriction on the lumen diameter in at least one of the major coronary artery.

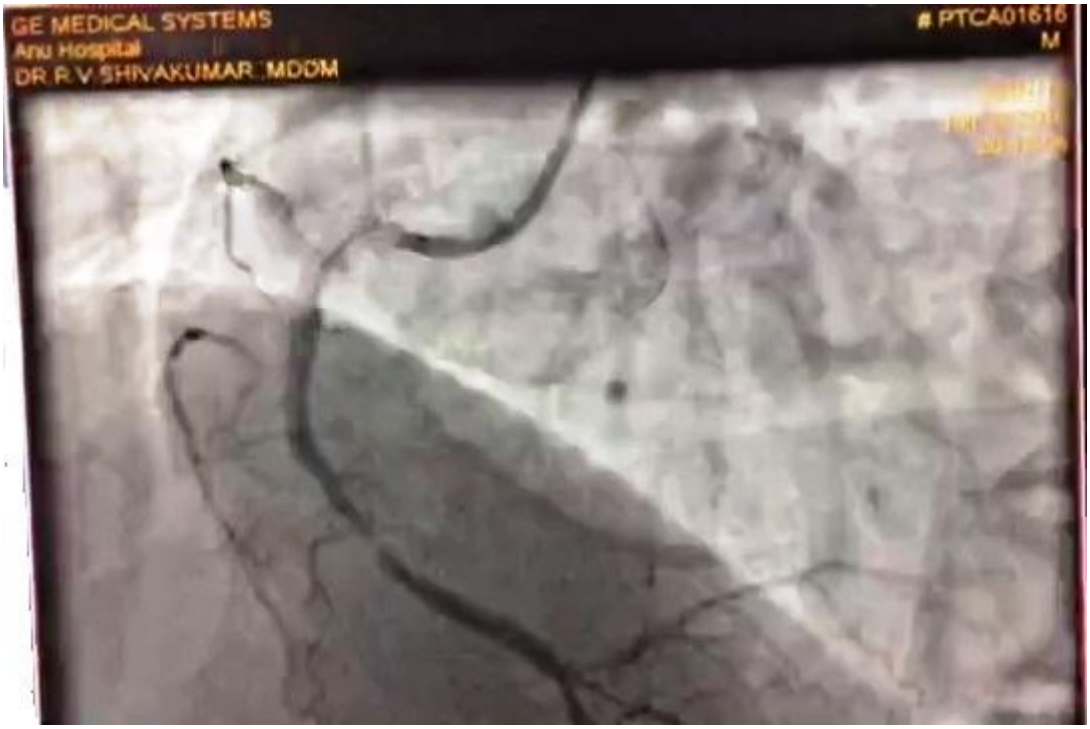


FIGURE 6: CORONARY ANGIOGRAM SHOWING STENOSIS >50% of RCA

Body Mass Index was calculated from the measured height and weight by using Quetelet's Index. BMI is measured by dividing weight in kilogram by height in meter square.[8]

The procedure was explained to all the people who participated in this study. Informed written consent was taken from both the controls and subjects.

RESULTS

The continuous variables were stated as mean ± standard deviation (SD) and matched up using student's t test between CAD and non-CAD groups. Categorical variables were described through frequency and percentage and were matched up among the above groups.

P value < 0.05 was considered to be statistically significant.

In this case control study, Eighty male subjects(n=80) were participated , which were divided into two groups, as Group A (n=40) and Group B (n=40). Group A includes forty control subjects and Group B includes forty CAD subjects who were referred for diagnostic Coronary Angiography. Serum Total Testosterone (ng/dL) level, FSH (mIU/ml) level and LH (mIU/ml) level were analyzed for Group A and Group B.

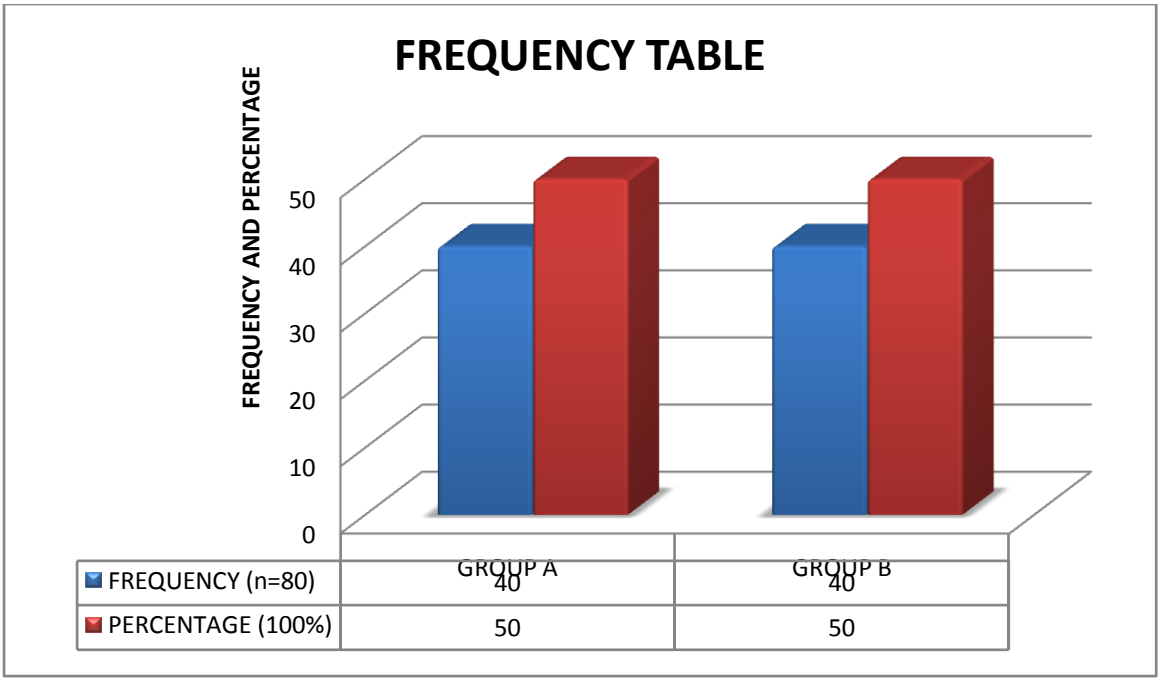


FIGURE 7

Figure 7 shows the Frequency and percentage of the subjects in this study. Group A has the frequency of n=40 and percentage of 50%. Group B has the frequency of n=40 and percentage of 50%.

DESCRIPTIVE STATISTICS:

MEAN VALUE FOR BOTH THE GROUPS

PARAMETERS	All group (n=80)			
	Minimum	Maximum	Mean	Standard Deviation
BMI	19.33	30.96	26.0139	2.28173
FSH (mIU/mL)	.15	41.71	6.9348	4.74030
LH(mIU/mL)	1.68	30.87	6.2873	3.41504
TESTOSTERONE (ng/ml)	.92	15.00	5.9018	2.69335

TABLE 1

Table 1 shows Mean and the Standard Deviation for BMI, FSH, LH and Testosterone for both the groups. BMI shows the mean value of 26.0139 ± 2.28173 for both the groups. FSH shows the mean value of 6.9348 ± 4.74030 for both the groups. LH shows the mean value of 6.2873 ± 3.41504 for both the groups. TESTOSTERONE shows the mean value of 5.9018 ± 2.69335 for both the groups.

T-TEST FOR GROUP A AND GROUP B:

GROUP	MEAN	S.D	T	DF	P VALUE
BMI					
A (n=40)	25.5165	2.22366	-1.986	78	.051>0.05 Not Significant
B (n=40)	26.5113	2.25700			
FSH (mIU/mL)					
A (n=40)	5.3955	1.58674	-3.054	78	.003<0.05 Significant
B (n=40)	8.4742	6.17565			
LH(mIU/mL)					
A (n=40)	5.0090	1.18101	-3.591	78	.001<0.05 Significant
B (n=40)	7.5655	4.34484			
TESTOSTERONE (ng/ml)					
A (n=40)	6.8365	2.32962	3.292	78	.001<0.05 Significant
B (n=40)	4.9670	2.73400			

TABLE 2

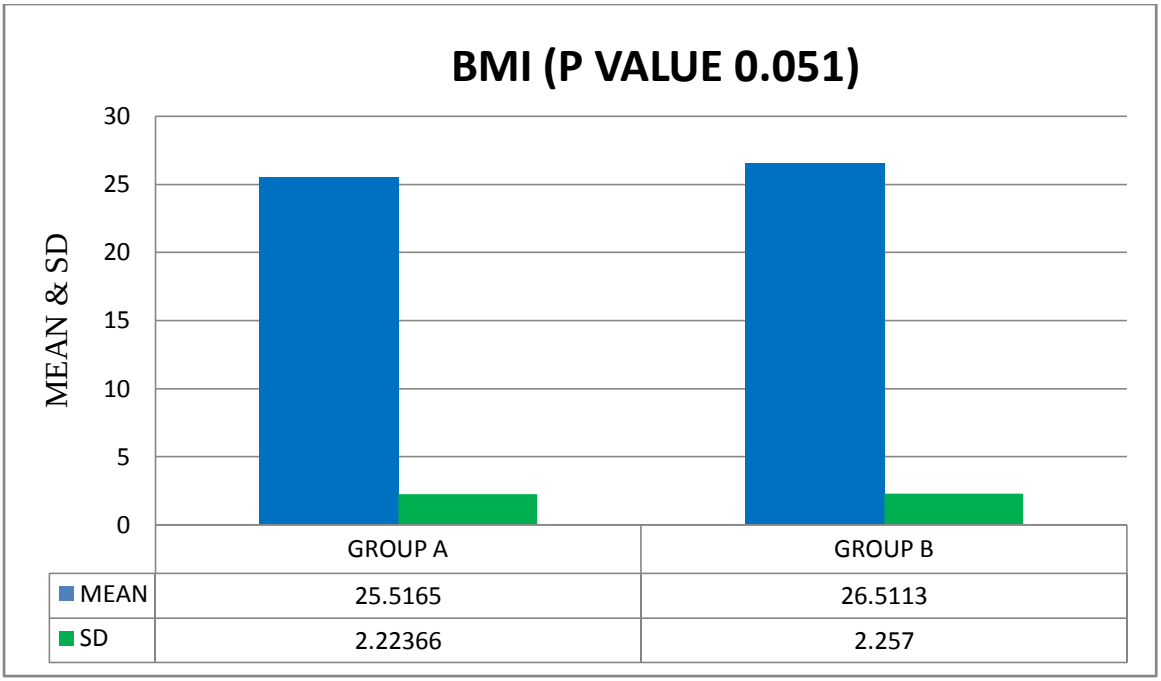
Table 2 shows t test for the parameters BMI, FSH, LH and Testosterone for both Group A and B. The mean BMI of 25.5165 ±2.22366 for Group A and the

mean BMI of 26.5113 ±2.25700 for Group B. The T = -1.986 with 78 degrees of freedom. The P value is 0.051(>0.05) which is not significant.

The mean FSH of 5.3955 ± 1.58674 for Group A and the mean FSH of 8.4742 ± 6.17565 for Group B. The T = -3.054 with 78 degrees of freedom. The P value is 0.003 (<0.05) which is significant.

The mean LH of 5.0090 ± 1.18101 for Group A and the mean LH of 7.5655 ± 4.34484 for Group B. The T = -3.591 with 78 degrees of freedom. The P value is 0.001 (<0.05) which is significant.

The mean TESTOSTERONE of 6.8365 ± 2.32962 for Group A and the mean TESTOSTERONE of 4.9670 ± 2.73400 for Group B. The T = 3.292 with 78 degrees of freedom. The P value is 0.001 (<0.05) which is significant.



. **FIGURE 8**

Figure 8 shows Mean and the Standard Deviation for BMI for both Group A and B. The mean BMI of 25.5165 ±2.22366 for Group A and the mean BMI of 26.5113 ±2.25700 for Group B. The P value is 0.051(>0.05) which is not significant.

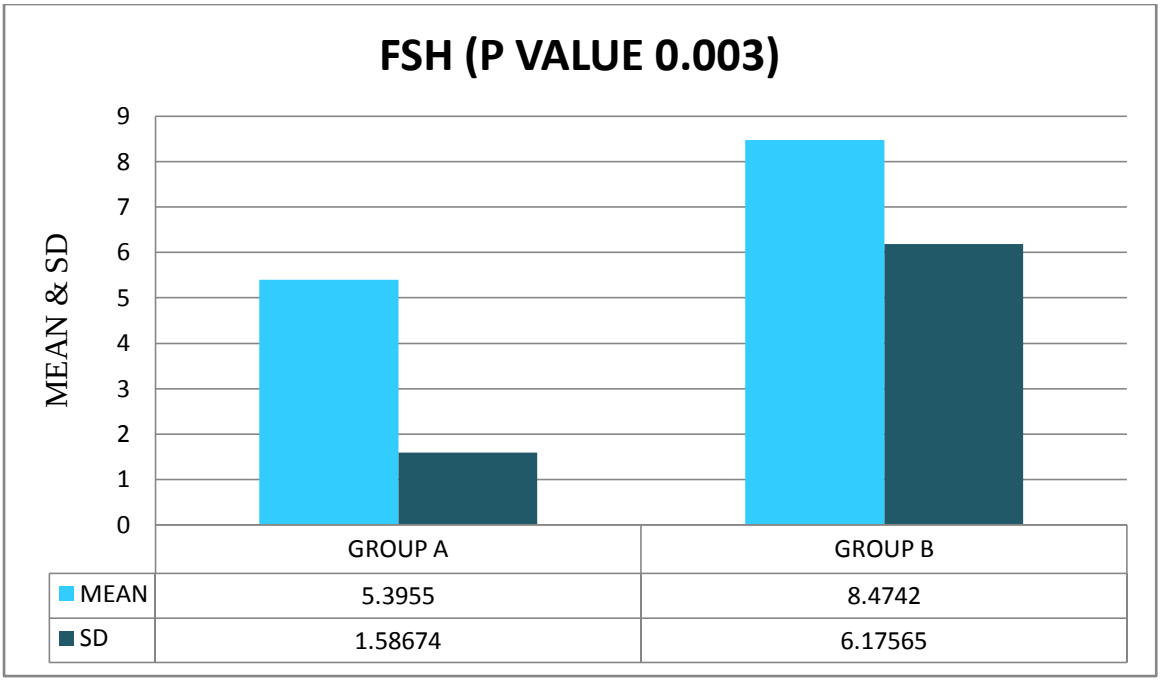


FIGURE 9

Figure 9 shows Mean and the Standard Deviation for FSH for both Group A and B. The mean FSH of 5.3955 ± 1.58674 for Group A and the mean FSH of 8.4742 ± 6.17565 for Group B. The P value is 0.003 (<0.05) which is significant.

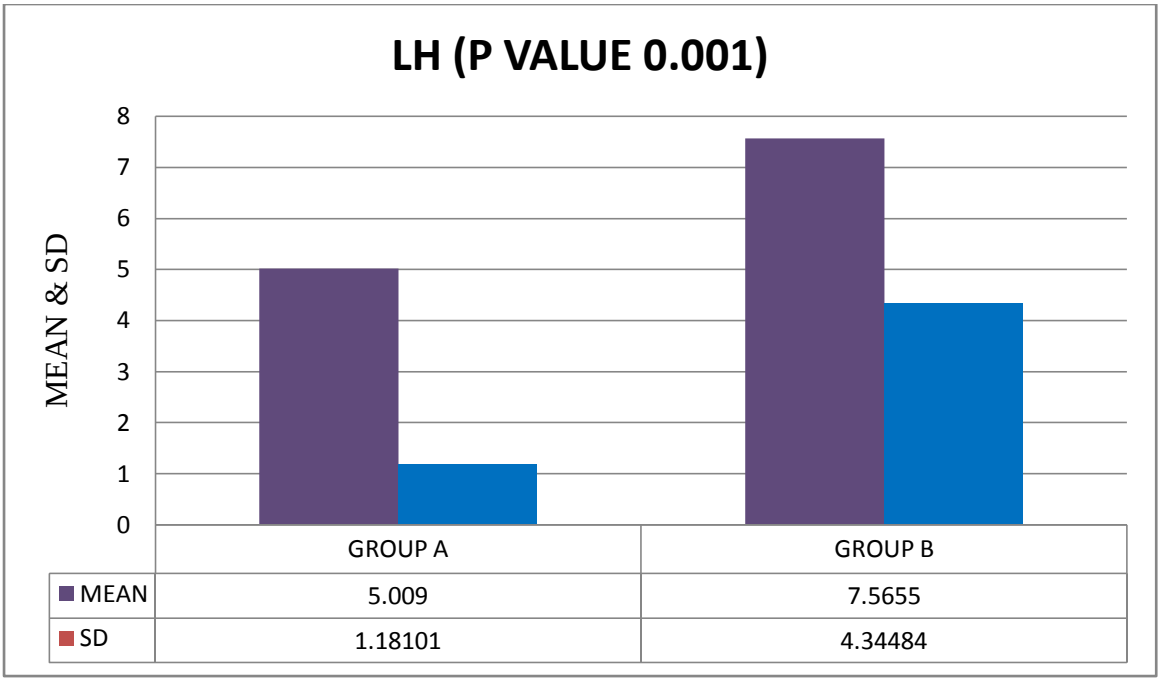


FIGURE 10

FIGURE 10 shows Mean and the Standard Deviation for LH for both Group A and B. LH shows the mean value of 6.2873 ± 3.41504 for both the groups. The mean LH of 5.0090 ± 1.18101 for Group A and the mean LH of 7.5655 ± 4.34484 for Group B. The P value is 0.001 (<0.05) which is significant.

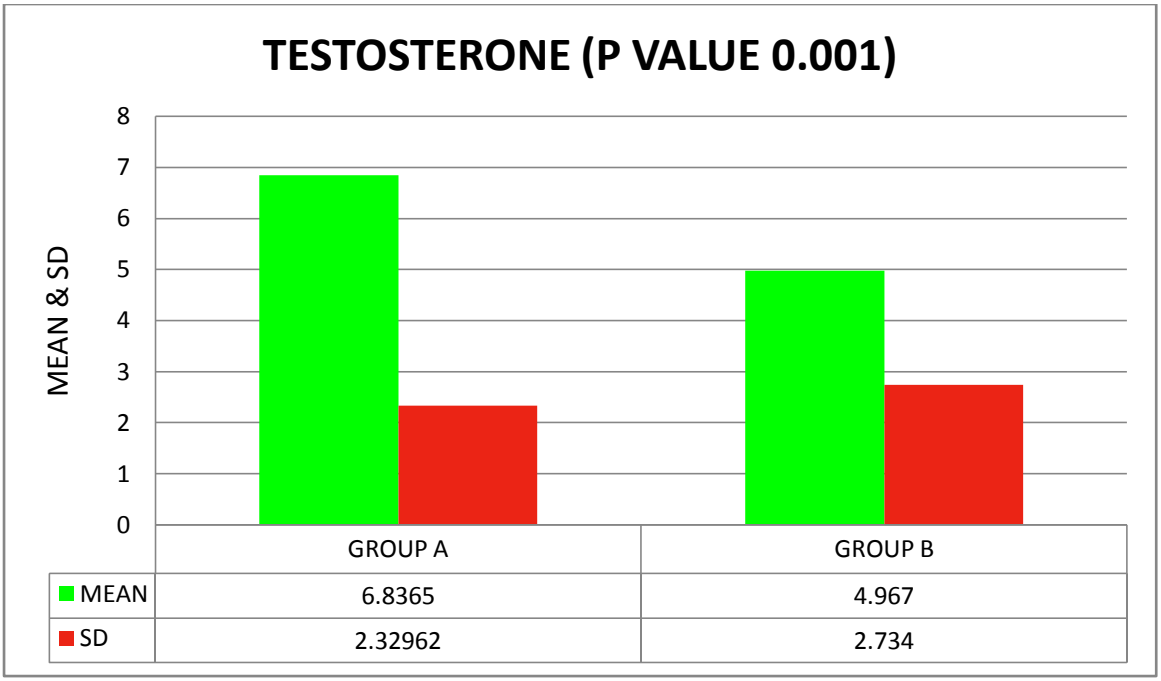


FIGURE 11

FIGURE 11 shows Mean and the Standard Deviation for TESTOSTERONE for both Group A and B. TESTOSTERONE shows the mean value of 5.9018 ± 2.69335 for both the groups. The mean TESTOSTERONE of 6.8365 ± 2.32962 for Group A and the mean TESTOSTERONE of 4.9670 ± 2.73400 for Group B. The P value is 0.001 (<0.05) which is significant.

DISCUSSION

Coronary Artery Disease is the most significant source in the world for Mortality and Morbidity. Men are prone to have Coronary Artery Disease earlier than the women[(2)].

Testosterone is the most powerful male sex hormone. Testosterone is formed mainly in the testis and secreted into the bloodstream where it flows and apply various effects in peripheral intended organs at different locations. Testosterone can carry out its specific task only by binding to the androgen receptor and before that it cannot be metabolized into estradiol by aromatase or into dihydrotestosterone by 5a-reductase. To sustain the proper concentrations of testosterone and its metabolites, a vibrant system of numerous interacting factors implicated relating the androgen-targeted organs has to be in ideal scale. [(4)]

The actions of testosterone in health and disease is very complicated. There is considerable support on the part of testosterone in aging men through metabolic syndrome and cardiovascular disease which has wholly altered its insight.[(32)]

Low Level of Testosterone concentration is considered as a threat feature for developing Coronary Artery Disease[(4)]. Mostly, men with increasing age who have Coronary Artery Disease, also have testosterone deficiency and symptoms of hypogonadism.[(70)]

In this study, Testosterone level was lower in Male patients with Coronary Artery Disease. The results of the Testosterone, FSH, LH and BMI were compared among the Men with Coronary Artery Disease and Healthy men of same age.

Statistically significant higher value of FSH and LH were found in Coronary Artery Disease patients than the Healthy Individuals in this present study.

It seems that **Phillips et al** found the correlations between testosterone level and Coronary Artery Disease, increases the possibility in men with hypotestosteronemia, is a threat to induce the Coronary Atherosclerosis who have undergone Coronary Angiography.[70]

This study results are similar with Case Control study of **English et al**, who used TT, FT, BT ,FAI for Analysis and measured Coronary artery disease which was confirmed by cardiac catheterization and found that men with Coronary Artery Disease have decreased concentration of BT, FT and FAI. And also higher levels of Follicle-Stimulating Hormone and Luteinizing Hormone.[43]

This study results are consistent with the study of **A.Alkamel et al**, who found that lower serum levels of Testosterone were significantly associated with premature CAD. This effect remained significant even after adjustment for other well-known cardiovascular threat features, which were also significant predictors of the presence of CAD.[71]

The results of the present study agreed with the study of **Zhao et al** (CCS, n=201), who used TT for Analysis. He measured Coronary artery disease by cardiac catheterization in Twenty seven patients and found that Men with Coronary artery disease have decreased levels of Total Testosterone.[42]

Dobrzycki et al[44], who used TT, FT, FAI for Analysis and measured Coronary artery disease, which was confirmed by cardiac catheterization and found

that Men with Coronary artery disease had decreased concentration of TT, FT, and FAI. Similar results were found in the present study.

Akishita et al[45] (CS, n=171),who used TT for study and Cardiovascular events were calculated by H&P, physician and hospital records. They found that Men with decreased concentration of TT were most probable to undergo the cardiovascular disease. The study results are consistent with the present study.

The present study results are parallel to the study of **GMC Rosano et al** (CCS, n=129), who confirmed that a significant correlation exists among testosterone level and the degree of coronary atherosclerosis, signifying that depleted testosterone levels may be one of the reasons preferably than the consequence of cardiovascular disease in men. He used TT, FT, BT, LH, FSH for Analysis. There were higher levels of Follicle-Stimulating Hormone and Luteinizing Hormone[46]

This study results are similar to the results of **Malkin et al**, who suggested that men with coronary artery disease have the increased frequency of testosterone deficiency, which is common.[57]

The result of the present study agreed with those of **Hu et al** (CCS, n=87), who used TT for Analysis. He measured cardiac catheterization confirmed Coronary artery disease and found that Men with Coronary artery disease have reduced concentration of Total Testosterone.[47]

But **Cauley et al**[48] and **Kabakci et al**[49] found that Testosterone level has no association with the Coronary Artery Disease.

Cauley et al[48] who used TT, FT for analysis and measured Coronary Artery Disease from nonlethal myocardial infarction, Deaths from Coronary Artery

Disease by the Records and ECG of the Hospital. They found that there was no changes in the levels of TT or FT. The main confounding features are Bio available Testosterone, which was not utilised for analysis and the Subjects did not go through Coronary Angiogram.

Kabakci et al.[49] who used TT, FT for analysis and measured Coronary Angiogram confirmed Coronary artery disease and found that there was no statistically significant changes in the levels of FT or TT. The potential confounding factors are that Bio available Testosterone was not utilised for the study and Free Testosterone was analysed by Suboptimal technique.

Our study reveals that BMI of Coronary Artery Disease patients are higher than the Healthy Individuals, but statistically insignificant.

Our study result is consistent with the study of **A.Alkamel et al**[71] compared BMI (Kg/m2) of Normal coronary subjects 25.82 ± 3.86 with CAD patients 26.30 ± 3.60 0.3 and found that it is statistically not significant.(P value - 0.3)

The result of the present study is similar with study of **GMC Rosano et al**[46], who compared CAD patient's BMI (kg/m2) 26.2 with normal subject's BMI 25.3 and found that it is statistically not significant.

Our study result is similar with the study of **Malkin et al**[57] matched BMI of normal coronaries 27.7 with the Coronary Disease 28.0 and concluded that it is statistically not significant.(P - 0.36)

Mulligan et al[65] evaluated 1326 normal men along with the 836 hypogonadal men. The average Body Mass Index was 31.5 for hypogonadal men, which was significant when compared with 28.5 for normal men.

Limitations:

The limitation of this study is that only Total Testosterone were used and Free testosterone, Bio-available Testosterone and other sex specific Hormones were not measured. Obesity was measured only by BMI. Waist Hip Ratio and estimated Visceral Adipose Tissue were not measured.

CONCLUSION

The correlation between Testosterone and Coronary Artery Disease is statistically significant, which lifts the likelihood that in men with hypotestosteronemia are at a risk to develop Coronary Artery Disease.

The specified evidences proposes that men with Coronary Angiogram Confirmed Coronary Artery Disease have decreased concentration of testosterone than the healthy men. The outcome of this study is consistent along with the evidences that lower levels of testosterone are related along with threat features of Coronary Artery Disease.

Currently, it is indefinite that whether low testosterone levels sources Coronary Artery Disease or lower concentration of testosterone are a corollary of Coronary Artery Disease.

Diminishing levels of testosterone in men are important in the development of osteoporosis, sexual dysfunction, and symptoms such as depression and fatigue as well, which needs additional evaluation..

Further studies can analyze the usage of exogenous testosterone in men and the efficacy of risk scoring method. These trials must be directed for increased threat men with Coronary Heart disease or Diabetes Mellitus or Hypertension or Dyslipidemia for the reason that these men have the largest part to benefit. The event rates of these men are more and any impact on the therapy, positive or negative is more likely to be established inside the borders of a clinical study.

Obesity can be measured by not only BMI, but also Waist Hip Ratio and estimated Visceral Adipose Tissue must be included in future studies.

BIBLIOGRAPHY

1. **Roger Detels, Robert Beaglehole, Mary Ann Lansang, Martin Gulliford.** Oxford Textbook of Public Health.5th. Oxford: Oxford University Press,2009.pp. 7,186. Vol. 1.

2. **Kanu Chatterjee, Mark Anderson, Donald Heistad, Richard E Kerber.** Cardiology- An Illustrated Textbook. 1st Edition. New Delhi : Jaypee Brothers Medical Publishers (P) Ltd, 2011. pp. 844-845.

3. **Valentin Fuster, Richard A Walsh, Robert A Harrington.** Hurst's The Heart. 13th Edition. China : The Mc Graw Hill Companies, 2011. pp. 17-19,24.

4. **J.Larry Jameson, Leslie J. De Groot.** Endocrinology- Adult and Pediatric. sixth Edition. Philadelphia : Elsevier, 2010. pp. 2469,2489. Vol. 2.

5. **Kim E. Barrett, Scott Boitano, Susan M. Barman, Heddwen L. Brooks.** Ganong’s Review of Medical Physiology. 23rd Edition. USA : The McGraw-Hill Companies, 2010. pp. 406-410,577-580.

6. **J.Topol, Eric.** Text Book of Cardiovascular Medicine. 3rd Edition. Philadelphia : Lippincott Williams & Wilkins, 2007. pp. 125-127.

7. **Emil A.Tanagho, Jack W.McAninch.** Smith's General Urology. 17th Edition. USA : The McGraw Hill Companies, 2008. pp. 717-721.

8. **Shlomo Melmed, Kenneth S.Polonsky, P.Reed Larsen, Henry M.Kronenberg.** Williams Textbook of Endocrinology. 12 Edition. Philadelphia : Elsevier, 2011. pp. 707-708, 1605.

9. **J.Wein, Alan.** Urology, Campbell - Walsh. 10th Edition. Philadelphia : Elsevier, 2007. p. 812. Vol. 1.

10. **Standring, Susan.** Gray's Anatomy. 40th Edition. SPAIN : ELSEVIER, 2008. pp. 1794-1799.

11. **Conti, C. Richard.** The Netter Collection OF MEDICAL ILLUSTRATIONS - Cardiovascular System. 2nd Edition. Philadelphia : Elsevier, 2014. pp. 14-15. Vol. 8.

12. **Prof.Dr.R.Vinodha M.D.,.** Applied Physiology Secrets. 1st Edition. New Delhi : Educreation Publishing, 2015. p. 58.

13. **Robert O. Bonow, Douglas L. Mann, Douglas P. Zipes, Peter Libby.** Braunwald's Heart Disease. 9th Edition. Philadelphia : Elsevier, 2012. pp. 914-930,1049,1213-1240.

14. **Walter F. Boron, Emile L. Boulpaep.** Medical Physiology. 2nd Updated Edition. Philadelphia : Elsevier, 2012. pp. 581-583,1093-1094.

15. **Arthur C. Guyton, John E. Hall.** Textbook of Medical Physiology. 12th Edition. Philadelphia : Elsevier, 2011. pp. 246-249,979-984.

16. **Sherwood, Lauralee.** Fundamentals of Human Physiology. 4th Edition. Canada : Brooks/Cole, Cengage Learning, 2012. pp. 252-257.

17. **Professor Parveen Kumar, Dr Michael Clark.** Kumar & Clarke's Clinical Medicine. 7th Edition. Spain : Elsevier, 2009. pp. 743-747.

18. **Prof.G.K.Pal.** Textbook of Medical Physiology. 2nd Edition. Delhi : Ahuja Publishing House, 2013. pp. 455-458.

19. **Francis S.Greenspan, David G.Gardner.** Basic & Clinical Endocrinology. 6th Edition. USA : The McGraw Hill Companies, 1997. pp. 424-426.

20. **Vermeulen A, Rubens R, Verdonck L.** Testosterone secretion and metabolism in male senescence. J Clin Endocrinol Metab 1972; 34: 730–5.

21. **Rubens R, Dhont M, Vermeulen A.** Further studies on Leydig cell function in old age. J Clin Endocrinol Metab 1974; 39: 40–5.

22. **Baker HW, Burger HG, de Kretser DM, Hudson B, O'Connor S.** Changes in the pituitary testicular system with age. Clin Endocrinol 1976; 5: 349–72

23 **Pirke KM, Doerr P.** Ages related changes in free plasma testosterone, dihydrotestosterone and oestradiol. Acta Endocrinol. 1975;80:171–178.

24. **Purifoy FE, Koopmans LH, Mayes DM.** Age differences in serum androgen levels in normal adult males. Hum Biol. 1981;53:499–511.

25. **Bremner WJ, Vitiello MV, Prinz PN.** Loss of circadian rhythmicity in blood testosterone levels with aging in normal men. J Clin Endocrinol Metab. 1983;56:1278–1281.

26. **Tenover JS, Matsumoto AM, Plymate SR, Bremmer WJ.** The effects of aging in normal men on bioavailable testosterone and luteinizing hormone secretion: response to clomiphene citrate. J Clin Endocrinol Metab. 1987; 65:1118–1126.

27. **Gray A, Berlin JA, McKinlay JB, Longcope C.** An examination of research design effects on the association of testosterone and male aging: results of a meta-analysis. J Clin Epidemiol 1991; 44: 671–84.

28. **Ferrini RL, Barrett-Connor E.** Sex hormones and age: a cross sectional study of testosterone and estradiol and their bioavailable fractions in communitydwelling men. Am J Epidemiol. 1998;147:750–754.

29. **Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR.** Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. J Clin Endocrinol Metab. 2001; 86:724–731.

30. **Njolstad I, Arnesen E, Lund-Larsen PG.** Smoking, serum lipids, blood pressure, and sex differences in myocardial infarction. A 12-year follow-up of the Finnmark Study. Circulation 1996; 93: 450–6.

31. **Raynor M, Mockford C, Boaz A.** Coronary heart disease statistics. London: British Heart Foundation; 1998.

32. **Jones, T.Hugh.** Testosterone Deficiency in Male. 1st Edition. Oxford : Oxford University Press, 2008. pp. 121-131.

33. **Barrett-Connor E, Khaw KT.** Endogenous sex hormones and cardiovascular disease in men. A prospective population-based study. Circulation. 1988; 78:539–545.

34. **Haffner SM, Mykkanen L, Valdez RA, Katz MS.** Relationship of sex hormones to lipids and lipoproteins in non-diabetic men. J Clin Endocrinol Metab 1993; 77:1610–1615.

35. **Simon D, Charles MA, Nahoul K, Orssaud G, Kremski J, Hully V, Joubert E, Papoz L, Eschwege E.** Association between plasma total testosterone and cardiovascular risk factors in healthy adult men: The Telecom Study. J Clin Endocrinol Metab 1997; 82:682–685.

36. **Dai WS, Gutai JP, Kuller LH, Laporte R, Falvo- Gerald L, Caggiula A.** Relation between plasma high-density lipoprotein cholesterol and sex hormone concentrations in men. Am J Cardiol 1984; 53:1259–1263.

37. **Heller RF, Wheeler MJ, Micallef J, Miller N, Lewis B.** Relationship of high density lipoprotein cholesterol with total and free testosterone and sex hormone binding globulin. Acta Endocrinol 1983;104:253–256.

38. **Hromadova M, Hacik T, Malatinsky E, Riecansky I.** Alterations of lipid metabolism in men with hypotestosteronemia. Horm Metab Res 1991;32: 392–394.

39. **Whitsel EA, Boyko EJ, Matsumoto AM, Anawalt BD.** Intramuscular testosterone esters and plasma lipids in hypogonadal men: a meta-analysis. Am J Med 2001;111: 261–269.

40. **Jaffe MD.** Effect of testosterone cypionate on post exercise ST segment depression. Br Heart J 1977;39: 1217–1222.

41. **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;85:269–272.

42. **Zhao SP, Li XP.** The association of low plasma testosterone level with coronary artery disease in Chinese men. Int J Cardiol. 1998;63:161–164.

43 **English KM, Mandour O, Steeds RP, Diver MJ, Jones TH, Channer KS.** Men with coronary artery disease have lower levels of androgens than men with normal coronary angiograms. Eur Heart J. 2000;21:890–894.

44. **Dobrzycki S, Serwatka W, Nadlewski S, Korecki J, Jackowski R, Paruk J, Ladny J, Hirnle T.** An assessment of correlations between endogenous sex hormone

levels and the extensiveness of coronary heart disease and the ejection fraction of the left ventricle in males. J Med Invest. 2003;50:162–169.

45. **Akishita M, Hashimoto M, Ohike Y, Ogawa S, Iijima K, Eto M, Ouchi Y.** Low testosterone level as a predictor of cardiovascular events in Japanese men with coronary risk factors. Atherosclerosis. 2010;210:232–236.

46. **Rosano G, Sheiban I, Massaro R, Pgnotta P, Marazzi G, Vitale C, Mercuro G, Volterrani M, Aversa A, Fini M.** Low testosterone levels are associated with coronary artery disease in male patients with angina. Int J Impot Res. 2007;19:176–182.

47. **Hu X, Rui L, Zhu T, Xia H, Yang X, Wang X, Liu H, Lu Z, Jiang H.** Low testosterone level in middle-aged male patients with coronary artery disease. Eur J Intern Med. 2011;22:133–136.

48. **Cauley JA, Gutai JP, Kuller LH, Dai WS.** Usefulness of sex steroid hormones levels in predicting coronary artery disease in men. Am J Cardiol. 1987; 60:771–777.

49. **Kabakci G, Yildirir A, Can I, Unsal I, Erbas B.** Relationship between endogenous sex hormones levels, lipoproteins, and coronary atherosclerosis in men undergoing coronary angiography. Cardiology. 1999;92:221–225.

50. **Arnlov J, Pencina MJ, Amin S, Nam BH, Benjamin EJ, Murabito JM, Wang TJ, Knapp PE, D'Agostino RB, Bhasin S, Vasan R.** Endogenous sex hormones and cardiovascular disease incidence in men. Ann Intern Med. 2006;145:176–184.

51. **Dunn JF, Nisula BC, Rodbard D.** Transport of steroid hormones: binding of 21 endogenous steroids to both testosterone-binding globulin and corticosteroid-binding globulin in human plasma. J Clin Endocrinol Metab. 1981; 53:58–68.

52. **Vermeulem A, Verdonck L, Kaufman JM.** A critical evaluation of simple methods for the estimation of free testosterone in serum. J Clin Endocrinol Metab. 1999;84:3666–3672.

53. **Shores MM, Matsumoto AM, Sloan KL, Kivlahan DR.** Low serum testosterone and mortality in male veterans. Arch Intern Med 2006; 166: 1660–5.

54. **Maggio M, Lauretani F, Ceda GP, Bandinelli S, Ling SM et al**. Relationship between low levels of anabolic hormones and 6-year mortality in older men: the aging in the Chianti Area (InCHIANTI) study. Arch Intern Med 2007; 167: 2249–54.

55. **Laughlin GA, Barrett-Connor E, Bergstrom J.** Low serum testosterone and mortality in older men. J Clin Endocrinol Metab 2008; 93: 68–75.

56. **Khaw KT, Dowsett M, Folkerd E, Bingham S, Wareham N et al**. Endogenous testosterone and mortality due to all causes, cardiovascular disease, and cancer in men: European prospective investigation into cancer in Norfolk (EPIC-Norfolk) Prospective Population Study. Circulation 2007; 116: 2694–701.

57. **Chris J Malkin, Peter J Pugh, Paul D Morris, Sonia Asif, T Hugh Jones, Kevin S Channer.** Low serum testosterone and increased mortality in men with coronary heart disease. Heart 2010;96:1821e1825. doi:10.1136/hrt.2010.195412

58. **Pugh PJ, Jones RD, West JN, Jones TH, Channer KS.** Testosterone treatment for men with chronic heart failure. Heart 2004; 90: 446–7.

59. **Jones TH, Arver S, Behre HM, Buvat J, Meuleman E et al.** Testosterone replacement in hypogonadal men with type 2 diabetes and/or metabolic syndrome (the TIMES2 study). Diabetes Care 2011; 34: 828–37.

60. **English KM, Steeds RP, Jones TH, Diver MJ, Channer KS.** Low-dose transdermal testosterone therapy improves angina threshold in men with chronic stable angina: A randomized, double-blind, placebo-controlled study. Circulation 2000 17;102: 1906– 11.

61. **Saad F, Aversa A, Isidori AM, Zafalon L, Zitzmann M et al.** Onset of effects of testosterone treatment and time span until maximum effects are achieved. Eur J Endocrinol 2011; 165: 675–85.

62. **Basaria S, Coviello AD, Travison TG, Storer TW, Farwell WR et al**. Adverse events associated with testosterone administration. New Eng J Med 2010; 363:109–22.

63. **Traish AM, Saad F, Feeley RJ, Guay A.** The dark side of testosterone deficiency: III. Cardiovascular disease. J Androl 2009; 30: 477–94.

64. **Lu-Yao GL, Albertsen PC, Moore DF, Shih W, Lin Y et al.** Survival following primary androgen deprivation therapy among men with localized prostate cancer. JAMA 2008; 300: 173–81

65. **Mulligan T, Frick MF, Zuraw QC, Stemhagen A, McWhirter C.** Prevalence of hypogonadism in males aged at least 45 years: the HIM study. Int J Clin Pract. 2006;60:762–769.

66. **Cunningham GR, Matsumoto AM, Swerdloff R.** Low testosterone and men's health. J Clin Endocrinol Metab. 2004;89.

67. **Kalyani RR, Gavini S, Dobs A.** Male hypogonadism in systemic disease. Endocrinol Metab Clin North Am. 2007;36:333–348.

68. **Spratt DI, Cox P, Orav J, Moloney J, Bigos T.** Reproductive axis suppression in acute illness is related to disease severity. J Clin Endocrinol Metab. 1993; 76:1548–1554.

69. **Beattie MC, Chen H, Fan J, Papadopoulos V, Miller P, Zirkin BR.** Aging and luteinizing hormone effects on reactive oxygen species (ROS) production and DNA damage in rat Leydig cells. Biol Reprod. 2013;88:100. doi: 10.1095/biolreprod.112.107052.

70. **Phillips GB, Pinkernell BH, Jing TY.** The association of hypotestosteronemia with coronary artery disease in men. Arterioscler Thromb 1994;14:701e6.

71. **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(8):** 545 – 550.

ANNEXURE

PROFORMA

TOPIC: ASSOCIATION BETWEEN TESTOSTERONE LEVEL AND CORONARY ARTERY DISEASE

Study Group/ Control Group

Name: **Age:** **Sex: Male**

Address: Occupation:

H/O Present illness:

Past History: HTN/DM/Cardiovascular Event/ Hypogonadism/ Hypopituitarism

Personal History: Smoking/ Alcohol/ Drug Intake

Family History:

General Examination:

Height: cm Weight: Kg BMI:

Anemia: Present/ Not Present

Cyanosis: Present/ Not Present

Clubbing: Present/ Not Present

Jaundice: Present/ Not Present

Pedal Edema: Present/ Not Present

Generalized Lymphadenopathy: Present/ Not Present

Vital signs:

PR: /min BP: mm Hg RR: /min

Examination of CVS:

Examination of RS:

Examination of Abdomen:

Examination of CNS:

Routine Investigation:

BLOOD SUGAR: UREA: URINE ALBUMIN: URINE SUGAR:

CRP:

CORONARY ARTERY STENOSIS: >50% / <50%

RESULTS:

PARAMETERS	CONTROL	CORONARY ARTERY DISEASE
Serum Testosterone (Ng/dL)		
Serum Follicle Stimulating Hormone (mIU/ml)		
Serum Luteinizing Hormone (mIU/ml)		
BMI (Kg/m^2)		

ABBREVIATIONS USED IN THE STUDY

CAD: CORONARY ARTERY DISEASE

LH: LUTEINIZING HORMONE

FSH: FOLLICLE-STIMULATING HORMONE

LCA: LEFT CORONARY ARTERY

RCA:RIGHT CORONARY ARTERY

LDL: LOW DENSITY LIPOPROTEIN

HDL: HIGH DENSITY LIPOPROTEIN

DHT: DIHYDROTESTOSTERONE

GnRH: GONADOTROPIN-RELEASING HORMONE

SHBG: SEX HORMONE-BINDING GLOBULIN

CCS: CASE CONTROL STUDY

CS: COHORT STUDY

TT: TOTAL TESTOSTERONE

FT: FREE TESTOSTERONE

BT: BIO AVAILABLE TESTOSTERONE

FAI: FREE ANDROGEN INDEX

H&P: HISTORY AND PHYSICAL EXAM

INFORMED CONSENT FORM

Dr.J.B.Ashraf Ali, Post graduate student in the Department of physiology, Thanjavur Medical college, Thanjavur, doing thesis on **"ASSOCIATION BETWEEN TESTOSTERONE AND CAD"**

I understand the procedure and voluntarily agree to participate in the study, I also understand that this study is a non-invasive procedure and the possible adverse effects have been explained to me in details clearly in my own language.

Signature of the subject

Name:

Place:

Date:

அராய்ச்சி ஒப்புதல் கடிதம்

அராய்ச்சி தலைப்பு: டெஸ்டோஸ்டிரோன் அளவு மற்றும் இருதய நாடி நோய்க்கு உள்ள தொடர்பு.

தஞ்சை மருத்துவக்கல்லூரி மருத்துவமனையில் ஆரோக்கியமான நபர்கள் மற்றும் தஞ்சையில் உள்ள இருதய நாடி நோயாளிகளுக்கு உள்ள டெஸ்டோஸ்டிரோன், பாளிக்கள் சிமுலேடிங் ஹார்மோன் மற்றும் லுடினைசிங் ஹார்மோன் ஆய்வு .

பெயர் : தேதி :

வயது : பால் :

ஆராய்ச்சி சேர்க்கை எண்:

இந்த ஆராய்ச்சியின் விவரங்களும் அதன் நோக்கமும் முழுமையாக எனக்கு தெளிவாக விளக்கப்பட்டது. எனக்கு விளக்கப்பட்ட விஷயங்களைப் பற்றி நான் புரிந்து கொண்டு எனது சம்மதத்தை தெரிவிக்கிறேன் .

இந்த ஆராய்ச்சியில் பிறரின் நிர்பந்தமின்றி என் சொந்த விருப்பத்தின் பேரில் நான் பங்கு பெறுகிறேன் மற்றும் நான் இந்த ஆராய்ச்சியிலிருந்து எந்நேரமும் பின் வாங்கலாம் என்பதையும் அதனால் எந்த பாதிப்பும் ஏற்படாது என்பதையும் நான் புரிந்துகொண்டேன். இந்த ஆராய்ச்சியினால் ஏற்படும் நன்மைகளையும் சில பக்கவிளைவுகளையும் பற்றி தெளிவாக மருத்துவர் மூலம் தெரிந்துகொண்டேன்.

நான் என்னுடைய சுயநினைவுடன் மற்றும் முழுசம்மதத்துடன் இந்த மருத்துவ ஆராய்ச்சியில் என்னை சேர்த்து கொள்ள சம்மதிக்கிறேன்.

ஆராய்ச்சியாளர் கையொப்பம் பங்கேற்பாளர் கையொப்பம்

நாள் :

இடம் :

ஆராய்ச்சி தகவல் தாள்

தஞ்சை மருத்துவக்கல்லூரி உடலியங்கியல் துறையில், டெஸ்டோஸ்டிரோன், பாளிக்கள் சிமுலேடிங் ஹார்மோன் மற்றும் லுடினைசிங் ஹார்மோன் ஆய்வு மேற்கொள்ளப்படுகிறது.

இந்த ஆய்வின் முடிவுகள் ஆரோக்கியமான நபர்கள் மற்றும் இருதய நாடி நோயாளிகளுக்கு உள்ள டெஸ்டோஸ்டிரோன், பாளிக்கள் சிமுலேடிங் ஹார்மோன் மற்றும் லுடினைசிங் ஹார்மோன் அளவில் உள்ள வேறுபாடுகளை வெளிப்படுத்தும்.

முடிவுகளை அல்லது கருத்துக்களை வெளியிடும்போதோ அல்லது ஆராய்ச்சியின்போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிடமாட்டோம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின் பேரில் தான் இருக்கிறது.

மேலும் நீங்கள் எந்நேரமும் இந்த ஆராய்ச்சியிலிருந்து பின் வாங்கலாம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

இரத்த பரிசோதனையின் முடிவுகள் ஆராய்ச்சியின்போதோ அல்லது ஆராய்ச்சியின் முடிவின் போதோதங்களுக்கு அறிவிக்கப்படும் என்பதையும் தெரிவித்துகொள்கிறோம்.

ஆராய்ச்சியாளர் கையொப்பம் பங்கேற்பாளர் கையொப்பம்

நாள் :

இடம் :

MASTER CHART

MASTER CHART					
S. NO	**Group**	**BMI**	**FSH (**mIU/mL)	**LH(**mIU/mL)	**TESTOSTERONE (**ng/ml)
1	A	22.21	2.97	3.24	3.74
2	A	27.7	8.87	7.8	3.09
3	A	25.14	2.25	4.97	1.89
4	A	20.83	8.99	5.05	2.61
5	A	26.63	3.54	4.92	2.74
6	A	25.56	9.91	8.8	3.21
7	A	19.33	4.72	4.8	3.8
8	A	24.16	3.47	5.18	4.3
9	A	24.69	8.4	3.6	11.58
10	A	25.96	6.4	4.6	5.7
11	A	23.52	4.5	5.4	6.2
12	A	26.79	6.1	6.3	7.2
13	A	23.03	5.5	5.6	6.9
14	A	25.71	3.9	4.6	5.3

15	A	25.71	4.4	5.4	5.8
16	A	25.72	4.3	4.7	6.4
17	A	27.28	4.6	3.9	7.2
18	A	29.17	5.9	5.8	5.9
19	A	24.62	5.1	4.7	6.4
20	A	24.09	4.9	5.8	6.8
21	A	26.87	6.2	6.3	7.9
22	A	23.03	3.6	4.6	8.5
23	A	24.68	5.7	3.6	8.9
24	A	29.41	4.8	4.5	9.6
25	A	23.8	5.6	3.5	7.5
26	A	25.84	5.6	4.8	7.8
27	A	25.59	4.9	5.1	6.9
28	A	24.22	5.8	6.2	8.9
29	A	26.5	6.9	5.6	11.2
30	A	25.52	6.6	6.1	9.2
31	A	27.55	4.5	3.7	6.8

32	A	23.22	5.5	4.2	8.7
33	A	27.81	5.4	4.1	7.5
34	A	24.52	4.3	5.6	6.9
35	A	29.03	4.6	3.5	7.6
36	A	24.44	4.6	3.2	9.1
37	A	27	5.7	6.5	8.7
38	A	28.9	5.2	4.3	9.4
39	A	26.49	6.1	5.4	9.1
40	A	28.39	5.5	4.4	6.5
41	B	24.91	0.637	3.16	11.58
42	B	25.8	4.8	11.24	2
43	B	25.03	0.151	3.57	15
44	B	27.66	12.21	11.94	7.22
45	B	27.94	1.42	1.68	0.92
46	B	26.07	5.31	7.76	3.72
47	B	26.67	3.66	5	3.41
48	B	30.96	5.35	13.6	1.35

49	B	28.86	41.71	30.87	3.03
50	B	28.78	11.09	7.48	7.47
51	B	26.42	3.1	5.54	4.96
52	B	23.22	12.93	10.28	2.6
53	B	30.83	11.2	4.8	4.7
54	B	25.61	10.5	7.8	2
55	B	28.01	11.5	6.7	7.6
56	B	26.37	11.6	7.6	7.22
57	B	24.52	6.8	6.7	0.92
58	B	29.4	7.8	7.1	3.72
59	B	25.6	8.4	8.9	3.41
60	B	26.98	9.5	7.4	1.35
61	B	25.63	10.2	6.9	3.03
62	B	26.29	9.7	6.8	7.47
63	B	23.38	7.8	6.5	5.7
64	B	29.38	7.4	6.1	6.7
65	B	23.23	7.4	5.8	5.6

66	B	23.88	9.2	6.4	4.7
67	B	28.69	8.4	6.8	3.5
68	B	25.9	7.8	8.1	4.7
69	B	30.52	9.6	7.2	5.3
70	B	24.12	10.2	7.8	5.4
71	B	25.63	8.4	6.1	4.8
72	B	28.31	7.6	6.8	6.1
73	B	26.03	8.5	6.2	4.5
74	B	22.32	7.5	7.4f	5.2
75	B	26.02	8.4	6.1	5.4
76	B	28.22	5.5	5.8	6.3
77	B	24.21	6.4	7.4	6.3
78	B	26.51	5.4	5.7	5.3
79	B	23.14	7.2	7.2	2.4
80	B	29.4	6.7	6.4	6.1