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THE RELATION BETWEEN LOW SERUM TESTOSTERONE LEVEL AND PERIPHERAL ARTERIAL DISEASE IN MEN AND CLINICAL EVALUATION OF EFFECT OF TESTOSTERONE ADMINISTRATION

Surgery

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ABSTRACT

Peripheral arterial disease (PAD) is most common among the men, especially chronic smokers and incidence in India is 1 in 5000 men. Multiple modalities of treatment available for the disease but many of them are expensive and cannot be performed in many patients due to various reasons. So our study assesses the association of testosterone to PAD and its use as a therapeutic drug. Testosterone causes vasodilation of the peripheral arteries by acting on the endothelium of the vessels and in turn results in release of nitric oxide (NO) which is a vasodilator and helps in vasodilatation of the vessels.[1-2]

The current study is being done to investigate a possible link between serum testosterone and lower extremity PAD in men and to know whether Short-term administration of testosterone induces a beneficial effect in men with peripheral artery disease. This effect may be related to direct peripheral artery-relaxing effects.

KEYWORDS

PAD, Peripheral arterial disease, testosterone levels, ABPI etc..,

INTRODUCTION:

NEED FOR THE STUDY:

Peripheral artery disease (PAD) is one of the most common manifestations of atherosclerosis, affecting about 27 million individuals in India, Europe and North America.[1] PAD is a powerful and independent risk factor of cardiovascular morbidity and mortality.[2-4] As an early indicator of PAD, a low ankle-brachial pressure index (ABPI) has also been associated with increased risk of subsequent cardiovascular disease (CVD) and mortality.[4]

Several prospective investigations have shown that low total testosterone (TT) concentrations in men were associated with a less favorable cardiovascular risk profile including obesity, incident metabolic syndrome, diabetes mellitus, dyslipidemia, hypertension, mortality and PAD.[5]

Given the suggested associations of testosterone, ABPI, and PAD with cardiovascular risk factors, morbidity, and mortality, it is intriguing that data relating circulating testosterone concentrations to ABPI and PAD are very limited. To date, there is only one cross-sectional study in elderly men reporting a positive correlation between low free testosterone concentrations and prevalent PAD.[6]

However, cross-sectional studies are limited in their ability to assess causality, and therefore no directionality for the observed association can be inferred from these studies. Thus evidence for a prospective association of sex hormones with PAD is lacking to date. Accordingly, we would investigate the associations of circulating testosterone concentrations with ABPI and PAD.

- Several lines of evidence support a role for testosterone in atherosclerotic disease in men. For example, several studies show an independent negative association between serum testosterone and male carotid artery atherosclerosis as well as cardiovascular disease.[6-8]
- Moreover, although no current evidence suggests that testosterone treatment affects the risk of cardiovascular disease.8Prevalence of cases of PAD with non-reconstructable critical limb ischemia is 13%.[5]
- The current study is being done to investigate a possible link between serum testosterone and lower extremity PAD in men and to know whether Short-term administration of testosterone induces a beneficial effect in men with peripheral artery disease. This effect may be related to a direct peripheral artery-relaxing effects
- The most common side effects related with testosterone administration are bladder contractions causing frequent passing of urine, urinary tract Infection, continued painful erection, enlarged breasts and few rare complications are adult respiratory distress Syndrome, liver Tissue death and high Cholesterol but all these side effects are found to occur when the dosage of testosterone given is 200-300 mg,IM, twice or thrice a week,but in our study the dosage given is 80 mg IM thrice a week which helps in sex independent vasodilation of peripheral arteries and the chances of complications to occur are very minimal and its safe for the patient.[9-11]

OBJECTIVES OF THE STUDY :

To assess the association between low serum testosterone level and peripheral artery disease in men.

To evaluate the effect of acute administration of testosterone on peripheral artery disease in men.

MATERIALS AND METHODS:

- **Source of data**

Patients coming to JSS hospital surgery out-patient and emergency department.

- **Study design:** Interventional study.
- **Sample size:** 50 pts
- Prevalence of peripheral arterial disease among males at our hospital in a year is 84 patients out of 1582 total admissions in the department of surgery. According to the formula my sample size comes to **50** patients.

Duration of study: 2 years (Sep 2013 to Sep 2015)

METHODS OF COLLECTION:

PROCEDURE:

Selection of patients coming with symptoms of peripheral arterial disease to the JSS OPD and Emergency Department. Patients will be included and excluded from the study depending on the below mentioned criterias:

Inclusion criteria:

1. All male patients with critical limb ischemia with ABPI <0.4.
2. All male patients where other treatment modalities available have failed or notfeasible.
3. All patients where bypass and endovascular cannot be performed due to foresaid reasons:

a) Patient not fit for surgery having other co-morbidities.
b) Financial constraints of the patient to undergo vascular procedures.
c) Outcome of the procedure is assessed to be very minimal.

Exclusion criteria:

1. All male patients with ABPI>0.4
2. All male patients where other conventional modalities of treatment are feasible.
3. All male patients with PAD associated with malignancies like carcinoma prostate, carcinoma lungs etc.

After examination of the patient either in OPD or Emergency department, ankle brachial pressure index will be assessed and depending on the value and other aspects of inclusion criteria patients

will be taken into study and patients will be given intramuscular injection of testosterone thrice a week for three weeks, after taking prior consent, and effect of the drug will be assessed depending on the improvement in the walking distance, ankle-brachial pressure index(ABPI) and symptomatic relief of pain will be assessed using pain scale of 0 to 10 (VAS). ABPI normal value is 1 and is described as ratio between the ankle pressure of either the dorsalispedis artery or posterior tibial artery whichever is more is taken as numerator and in the denominator the brachial pressure of the arm is taken whichever is higher. ABPI of 1 is normal, 0.7-0.9 is moderate ischemia, 0.4-0.6 is severe ischemia and < 0.4 is critical limb ischemia.[11]

STATISTICAL METHODS:-

- **Descriptive statistics** is done measuring mean, standard deviation and proportions with 95% confidence interval.
- **Independent t test**
- **Paired t test** . P value <0.05 is considered as statistically significant.
- **Mcnemartest , p<0.00001.**
- **Mann Whitney test, P<0.0001.**
- **Chi-square test**
- Cross-tabulation (contingency co-efficient test) will be analyzed using SPSS version 18

RESULTS AND OBSERVATIONS:

GRAPH 1: GRAPH SHOWING AGEDISTRIBUTION OF STUDY SUBJECTS

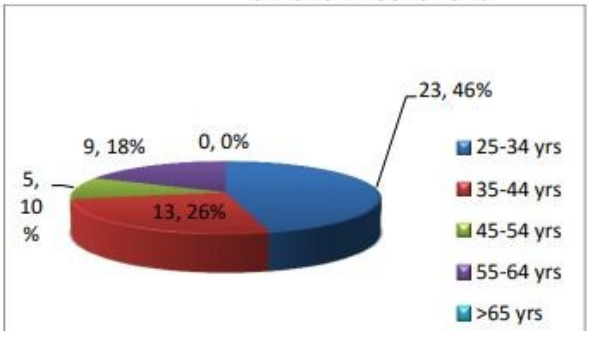
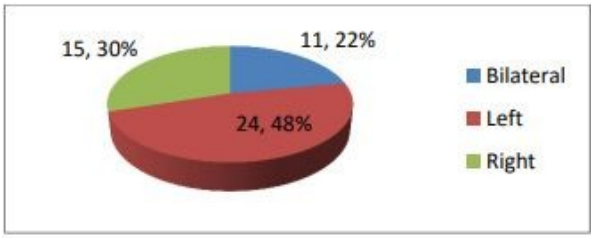


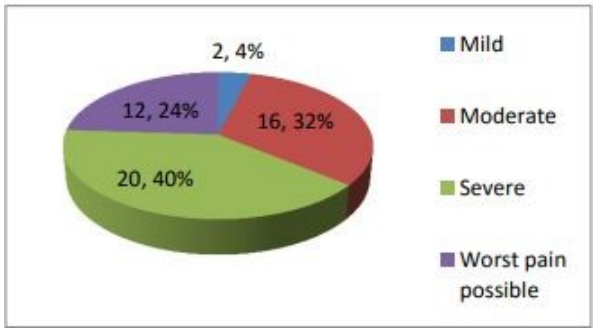
Table 1: MEAN AGE IN CASES

	PAD	
	Mean	SD
Age	38	16.1

GRAPH 2:SYMMETRY OF PAD INVOLVEMENT OF STUDY



GRAPH 3: VAS SCORE FOR PAIN AT ADMISSION



GRAPH 4: WALKING ABILITY OF CASES BEFORE TREATMENT

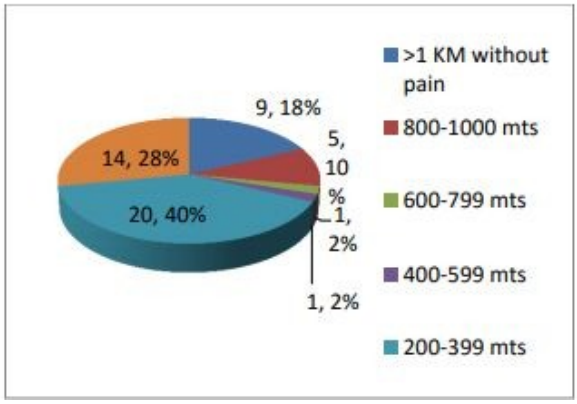


Table 2: FREE TESTOSTERONE LEVELS AMONG STUDY PATIENTS

Free testosterone level	Count	%
Decreased	44	88
Normal	6	12
Increased	0	0
Total	50	100

Table 3: DISTRIBUTION OF ABPI AMONG STUDY SUBJECTS.

ABPI at presentation

Mean	N	Std. Deviation
0.298	50	0.08816

Table 4: ASSOCIATION OF TESTOSTERONE LEVELS WITH SEVERITY OF PAD

	ABPI at presentation Count %			95% Confidence Interval for Mean%	
	N	Mean	Std. Deviation	Lower Bound	Upper Bound
Decreased	44	0.2932	0.08815	0.2664	0.32
Normal	6	0.3333	0.08733	0.2417	0.425
Total	50	0.298	0.08816	0.2729	0.3231

In our study subjects 46 % of the subjects were in the age group of 25 to 34 years and among them 88 % of the subjects had decreased testosterone levels as compared to the normal range for their specified age. Initially when the patient presented the pain was graded depending on the visual analogue scale and 40 % of the subjects had severe pain 32% had moderate pain and 24% of the subjects had worst possible pain, and after administration of testosterone there was drastic improvement in subjects with worst possible pain where in only 2 % of the subjects had this type of pain after treatment, and the percentage of patient having severe pain, also decreased to 22 % but there was no definite improvement in people with moderate pain, the reason of which is not known and has to be investigated. On initial assessment there were 28% of the patients who were not able to walk for more than 200 meters but after testosterone administration reduced to 10% which was significant statistically with P value <0.0001.Initially there were 9 (18%) study subjects out of fifty who were able to walk a distance of > 1km after the testosterone administration the number increased to 13 (26%) which is very significant.

All the subjects had significant improvement in walking distance post testosterone administration. The mean ABPI of the subjects at the time of admission was 0.298 and the mean ABPI after testosterone administration had gone upto 0.463 which is 64% improvement which is remarkable. All these study results amounts to immense benefit for the patients with critical limbischemia in whom advanced surgical procedure could not be implicated for the reason previously mentioned and the patient had significant improvement in the walking distance and the pain threshold which definitely improve the quality of life of a person with real agony.

Table 5: DEGREE OF PERCENTAGE IMPROVEMENT IN ABPI AFTER TREATMENT.

Statistic Percentage Mean 35.7			
improvement	95% Confidence Interval for Mean	Lower Bound	30.8314
		Upper Bound	40.5686

Table 6: PERCENTAGE CHANGES IN WALKING DISTANCE AFTER TESTOSTERONE INTECTIONS

Walking distance	Before treatment		After 9 doses of testosterone	
	N	%	N	%
>1 KM without pain	9	18	13	26
800-1000 mts	5	10	3	6
600-799 mts	1	2	5	10
400-599 mts	1	2	12	24
200-399 mts	20	40	12	24
<200 mts	14	28	5	10
Total	50	100	50	100

Table 7: PERCENTAGE CHANGES IN PAIN AS VAS AFTER TESTOSTERONE ADMINISTRATION

VAS	Before treatment		After 9 doses of testosterone	
	N	%	N	%
Mild	2	4	20	40
Moderate	16	32	18	36
Severe	20	40	11	22
Worst pain possible	12	24	1	2

DISCUSSION:

Accumulating data support a role for circulating testosterone in Peripheral arterial disease in men... We show here that circulating free testosterone positively associates with ABPI indicating a positive association between testosterone and the degree ofatherosclerotic disease in the lower extremities. Furthermore, when lower extremity PAD was defined as an ABPI < 0.90, we found that low free testosterone associate with lower extremity PAD.

In our study subjects 46 % of the subjects were in the age group of 25 to 34 years and among them 88 % of the subjects had decreased testosterone levels as compared to the normal range for their specified age. Initially when the patient presented the pain was graded depending on the visual analogue scale and 40 % of the subjects had severe pain 32% had moderate pain and 24% of the subjects had worst possible pain, and after administration of testosterone there was drastic improvement in subjects with worst possible pain where in only 2 % of the subjects had this type of pain after treatment, and the percentage of patient having severe pain alsodecreased to 22 % but there was no definite improvement in people with moderate pain ,the reason of which is notknown and has to be investigated. On initial assessment there were 28% of the patients who were not able to walk for more than 200 meters but after testosterone administration reduced to 10% which was significant statistically with P value <0.0001.Initially there were 9 (18%) study subjects out of fifty who were able to walk a distance of > 1km after the testosterone administration the number increased to 13 (26%) which is very significant. All the subjects had significant improvement in walking distance post testosterone administration .The mean ABPI of the subjects at the time of admission was 0.298 and the mean ABPI after testosterone administration had gone up to 0.463 which is 64% improvement which is remarkable. All these study results amounts to immense benefit for the patients with critical limb ischemia in whom advanced surgical procedure could not be implicated for the reason previously mentioned and the patient had significant improve in the walking distance and the pain threshold which definitely improve the quality of life of a person with real agony.
Our data are in accordance with accumulating evidence suggesting that endogenous testosterone detrimentally affect atherosclerosis and circulating testosterone independently predicts the progression of peripheral arterial disease in men. Furthermore, serum testosterone levels decreased in subjects with coronary heart disease in a case-control study of men in the Framingham cohort. In addition, another study coupled the CC genotyptostee of the testosterone receptor alpha c.454-397T_C polymorphism, possibly associated with enhanced receptor function, with increased incidence of peripheral arterial disease in men.

Furthermore, a recent population-based study suggested that endogenous free testosterone levels assosciated with lower risk for cardiovascular events in men .One might speculate that the effects of testosterone on peripheral arterial disease might differ depending on the stage of the disease.Clearly, the impact of testosterone on peripheral arterial disease in men requires further investigation. The present study reports for the first time a positive association between serum testosterone levels and lower extremity PAD in men.

However, previously studies have established a significant relationship between circulating testosterone and incident cardiovascular events in men but not with regard to peripheral arterial disease. In most animal studies, testosterone treatment inhibits atherosclerosis in males; and testosterone (high dose) is a coronary vasodilator in men with established atherosclerosis. However, no current interventional study has sufficient power to assess a possible protective effect of testosterone on human atherosclerosis or cardiovascular disease.

In comparison, previous data from the MrOS Sweden cohort demonstrate that testosterone associate positively in peripheral arterial disease in men. The more precise role of testosterone as well as its precursors and derivatives in the human peripheral arterial disease process requires future research. Although low free and total testosterone yielded similar ORs for lower extremity PAD, the significance of free testosterone levels in the blood carries more significance. Thus, our results could reflect association between testosterone and PAD and also significant improvement after testosterone administration.

CONCLUSION:

The present study compares the association between free testosterone levels in the body and PAD in men which has been one of the unexplored fiels till now in peripheral arterial disease.The effect of testosterone on human vascular function is a complex issue and may be dependent upon the underlying androgen and/or disease status. Although not definitive, the majority of studies suggest that testosterone may display both acute and chronic vasodilatory effects upon various vascular beds at both physiological and supraphysiological concentrations and via endothelium-dependent and -independent mechanism. In addition, testosterone may also chronically condition vessel response to other vasoactive agents to influence reactivity, with treatment in testosterone-deficient men potentially restoring vascular function. Concurrently, testosterone has demonstrated anti-inflammatory effects clinically and testosterone can improve atherosclerosis assessed non-invasively in hypogonadal men and in animal studies. Although conflicting and contradictory experimental evidence exists, testosterone can influence cell-specific vascular inflammation and may potentially be a mechanism by which testosterone protects against atherogenesis in animal models. Testosterone may, therefore, alleviate the hemodynamic symptoms of atherosclerosis and improve atherosclerotic outcomes associated with disturbed flow patterns and dysfunctional vascular reactivity and offer potential therapeutic benefits for PAD. The mechanism of the action of testosterone on vascular cells remains unknown but may include classical steroid receptor activation and modulation of gene transcription (genomic), AR-mediated activation of rapid intracellular signaling pathways (non-genomic), direct ion channel modulation and/or activation of a thus far unknown membrane receptor to elicit these effects on vascular function and vascular inflammation.

And also in our present study there was significant improvement in patients :

- Pain threshold
- Walking distance
- ABPI.

However, the current scientific literature supports firstly the notion that testosterone is a vascular hormone that does affect vasoreactivity and secondly that testosterone can beneficially enhance biological processes involved in atheroprotection, in particular, lipid deposition and inflammation both within the arterial wall and in the circulation. Clinical studies have shown benefits for up to one year for cardiac ischaemia and its symptom of angina, cardiac failure and certain cardiovascular risk factors but with regard to peripheral arterial disease nothing much has been studied. While testosterone has therapeutic potential as a vascular hormone, further large randomised placebo-controlled trials are required to elucidate its long-term clinical

relevance to Peripheral arterial disease in men. Whether or not testosterone directly protects against peripheral arterial diseas and reduces complications including mortality, therefore warrants further investigation, and the complex underlying vascular mechanisms of action require clarification.

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