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General Surgery

CORRELATIONS OF ENDOGENOUS TESTOSTERONE AND DHEA-S IN PERIPHERAL ARTERIAL DISEASE

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ABSTRACT **Background:** Peripheral arterial disease is Occlusive disease of the arteries of the extremity. Common causes are Atherosclerosis (most common), Buerger's disease, vasculitis and other arteritis, thromboembolism etc. Peripheral arterial disease (PAD) is a treacherous disease as it remains asymptomatic for so long. As PAD progresses, it may lead to classical intermittent claudication and critical limb ischemia. DHEAS has been demonstrated to have an antiatherosclerotic effect by prevention of platelet aggregation, uptake of cholesterol and a decrease in the proliferation of vascular smooth muscle cells. 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 vasodilation. Testosterone suppresses expression of vascular cell adhesion molecule-1 (proinflammatory cytokines), anti-inflammatory factors by its derivative 5-dihydrotestosterone which is the earliest step in atherosclerosis. Interestingly Testosterone and DHEAS also has beneficial effects on cardiac ischemia, angina and chronic heart failure. The aim of this study is to look for any relationship of Testosterone and DHEAS in Peripheral Arterial Disease. **Methods:** Total 50 patients both inpatients and outpatients were studied. The period of study was from September 2016 to June 2018. Patients who were proven to have peripheral arterial disease on colour doppler were taken for study. The study was done to look if any relationship is present between serum testosterone and dehydroepiandrosterone sulfate (DHEA-S) in a peripheral arterial disease patients. Data were documented and stored in a proper database format. At the end of data collection from the samples, data analysis was done using SPSS 16 software and appropriate tests of significance were applied. For categorical variables Chi-square test and Fischer's Exact test was used. For comparing two groups of mean student's t-test was used. To correlate more than two continuous data Pearson and Spearman Correlation Coefficient was used. P value <0.05 considered as statistically significant. **Results:** Our results showed that total serum testosterone and DHEA-S were not significantly decreased in PAD patients in comparison to the control group. We could not observe any significant correlation. **Conclusion:** These results express that there is no significant correlation of Serum Testosterone and Dehydroepiandosterone with Peripheral arterial Disease. In our study there are significant correlations with inflammatory markers (C reactive protein, Interleukin6, Homocysteine) Lipid profile (cholesterol, Triglyceride, HDL, VLDL) and HbA1C with serum Testosterone and Dehydroepiandosterone in Peripheral Arterial Disease.

KEYWORDS :

Introduction

Peripheral arterial disease is Occlusive disease of the arteries of the extremity. Common causes are Atherosclerosis (most common), Buerger's disease, vasculitis and other arteritis, thromboembolism etc (1-3). Basically, there is arterial narrowing may be due to atherosclerosis, stenosis, occlusion, emboli, thrombus, inflammation of vessels wall(vasculitis) which causes decreased blood flow to muscles. Peripheral arterial disease (PAD) is a treacherous disease as it remains asymptomatic for so long (4,5). As PAD progresses, it may lead to classical intermittent claudication and critical limb ischemia. The majority of PAD patients die of cardiac and cerebrovascular-related events. The Prevalence of PAD with non-reconstructable critical limb ischemia is 13% and the 5-year mortality of PAD patient is 15-30%. Few studies show that Testosterone and DHEAS both having effect on endothelium of blood vessels. Both hormones decrease with old age (6).

DHEAS has been demonstrated to have an antiatherosclerotic effect by prevention of platelet aggregation, uptake of cholesterol and a decrease in the proliferation of vascular smooth muscle cells. It causes dilatation of the vessels in animal models and also increases nitric oxide synthase activity and nitric oxide production by either genomic or nongenomic mechanisms within the vascular endothelium. It also regulates the synthesis of vasoconstrictor, endothelin-1 and protects endothelial cells against apoptosis.

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 vasodilation. Testosterone suppresses expression of vascular cell adhesion molecule-1 (proinflammatory cytokines), anti-inflammatory factors by its derivative 5-dihydrotestosterone which is the earliest step in atherosclerosis. Interestingly Testosterone and DHEAS also has beneficial effects on cardiac ischemia, angina and chronic heart failure. The aim of this study is to look for any relationship of Testosterone and DHEAS in Peripheral Arterial Disease (7,8).

Material And Methods

The study was conducted in the Department of General Surgery, Sir Sunderlal Hospital, Institute of Medical Sciences (IMS), BHU, Varanasi, in collaboration with Department of Endocrinology. Total 50 patients both inpatients and outpatients were studied. The period of study was from September 2016 to June 2018. Patients who were proven to have peripheral arterial disease on colour doppler were taken for study.

Material:
Informed and written consent was taken from every case. Clinical assessment of all patients, detailed history and physical examination was performed and recorded in proforma. After proper history and clinical examination of the patient either in OPD or in patient department, ankle brachial pressure index was assessed. Blood sample was collected for serum testosterone (empty stomach before 9AM) and serum DHEA chemiluminescence immunoassay (Beckman Coultor, USA). Blood samples were also used for various haematological and biochemical parameters. Serum sample was obtained by centrifugation and stored at –20°C. Levels of serum testosterone and DHEAS assessed and correlated with peripheral arterial disease.

Access DHEA-S Reagent
- R1a: Paramagnetic particles coated with goat anti-rabbit IgG: rabbit anti DHEA-S in TRIS buffered saline, with surfactant, bovine serum albumin (BSA), < 0.1% sodium azide, and 0.1% ProClin 300.
- R1b: DHEA-S-alkaline phosphatase (bovine) conjugate in TRIS buffered saline, with surfactant, BSA matrix, < 0.1% sodium azide, and 0.1% ProClin 300.

Access Testosterone Reagent
- R1a: Paramagnetic particles coated with goat anti-mouse IgG; testosterone alkaline phosphatase conjugate with bovine serum albumin (BSA), < 0.1% sodium azide, and 0.1% ProClin 300.
- R1b: Sample Treatment Solution, < 0.1% sodium azide.
- R1c: Monoclonal anti-testosterone (mouse), protein (BSA, mouse, goat), < 0.1% sodium azide, 0.1% ProClin 300

Method:
Principles of the Procedure Access DHEA-S assay
The Access DHEA-S assay is a competitive binding immunoenzymatic assay. A sample is added to a reaction vessel with paramagnetic particles coated with goat anti-rabbit: rabbit anti-DHEA-S and DHEA-S alkaline phosphatase conjugate in TRIS-buffered protein solution. After incubation in a reaction vessel, materials bound to the solid phase are held in a magnetic field while unbound materials are washed away. Then, the chemiluminescent substrate Lumi-Phos 530 is added to the vessel and light generated by the reaction is measured with a luminometer. The light production is inversely proportional to the concentration of DHEA-S in the sample. The amount of analyte in the sample is determined from a stored, multi-point calibration curve.

Principles of the Procedure Access Testosterone assay
The Access Testosterone assay is a competitive binding immunoenzymatic assay. A sample is added to a reaction vessel along with Sample Treatment Solution, mouse monoclonal anti-testosterone antibody, testosterone alkaline phosphatase conjugate, and paramagnetic particles coated with goat anti-mouse polyclonal antibody. Testosterone in the sample is released from the carrier proteins by the Sample Treatment Solution and competes with the testosterone alkaline phosphatase conjugate for binding sites on a limited amount of specific anti-testosterone monoclonal antibody. The resulting antigen-antibody complexes are then bound to the solid phase by the capture antibody. After incubation in a reaction vessel, materials bound to the solid phase are held in a magnetic field while unbound materials are washed away. Then, the chemiluminescent substrate Lumi-Phos 530 is added to the vessel and light generated by the reaction is measured with a luminometer. The light production is inversely proportional to the concentration of testosterone in the sample. The amount of analyte in the sample is determined from a stored, multi-point calibration curve.

Normal Range:
Testosterone
- Male (21-45years) = 6.4-31.6nmol/L
- >45 years = decreased by 1%per year
- Female adult = 0.2-4.4nmol/L

Dehydroepiandosterone
- Male = 10-619µg/dL
- Female (premenopousal) = 12- 535µg/dL
- Female (postmenopousal) = 30-260 µg/dL

Statistical Analysis:
Data were documented and stored in a proper database format. At the end of data collection from the samples, data analysis was done using SPSS 16 software and appropriate tests of significance were applied. Data were checked for the assumption of normality. Few of the data did not follow Gaussian distribution curve, hence we opted for non-parametric tests like Kruskal Wallis tests, Mann-Whitney U test, Wilcoxon signed-rank test. For categorical variables Chi-square test and Fischer's Exact test was used. For comparing two groups of mean student's t-test was used. To correlate more than two continuous data Pearson and Spearman Correlation Coefficient was used. P value <0.05 considered as statistically significant.

Observation
Total no. of patients who were part of this study are 50, out of which 56% (n=28) were diagnosed as Atherosclerotic disease, 10% (n=5) patients Buerger's disease, 14% (n=7) Vasculitis, 20% (n=10) Thromboembolism (Table 1)

Table 1: Distribution of Cases according to Diagnosis

Diagnosis	Frequency	Percent
Atherosclerosis	28	56.0
Buerger's disease	5	10.0
Vasculitis	7	14.0
Thromboembolism	10	20.0
Total	50	100.0

Our study shows that 3 patients of atherosclerotic disease, 2 patient of Buerger's disease, 1 of Vasculitis and of 1patient of Thromboembolic disease were less than 40 years. 6 patients of atherosclerotic disease, 1 of Buerger's disease, 1 of Vasculitis, 4 of Thromboembolic disease were between 41-50 years. 7 patients of Atherosclerotic disease, 1 of Buerger's disease, 2 of Vasculitis, 3 Thromboembolic diseases were in 51-60 years age group. 6 patients of atherosclerotic disease, 1 of Buerger's disease, 2 of Vasculitis 2 of Thrombo embolic disease were in 61-70 years age group. 6 patient of atherosclerosis and 1 patient of Vasculitis more than 70 disease, years of age. Youngest patient in atherosclerotic disease was 48 years and oldest of 88 years, youngest patient of Buerger's disease was 38 years age and oldest of 61 years. Youngest patient of Vasculitis was 17 years age and oldest of 74 years. Youngest patient of Thromboembolic disorder was 37 years age and oldest of 69 years age (Table-2)

Table 2: Age Distribution in various groups

Age group (yrs)	Diagnosis			
	Atherosclerosis (n=28)	Buerger's disease (n=5)	Vasculitis (n=7)	Thromboembolism (n=10)
	No. (%)	No. (%)	No. (%)	No. (%)
≤40	3(10.7)	2 (40.0)	1 (14.3)	1(10)
41-50	6(21.4)	1 (20.0)	1 (14.3)	4(40)
51-60	7 (25)	1 (20.0)	2 (28.6)	3(30)
61-70	6 (21.4)	1 (20.0)	2 (28.6)	2(20.0)
≥70	6 (21.4)	0 (0.0)	1 (14.3)	0 (0)

$\chi 2 = 5.381$; $p = 0.963$

In our study 21(75%) patients of atherosclerotic disease, all patient male Patients of Buerger's disease, 5(71.4%) patient of Vasculitis and 7(70%) patient of Thromboembolic disorder were male (Table-3).

Table 3: Sex Distribution in various groups

Sex	Diagnosis			
	Atherosclerosis n=28	Buerger's disease n=5	Vasculitis n = 7	Thromboembolism n=10
	No. (%)	No. (%)	No. (%)	No. (%)
Male	21 (75)	5 (100.0)	5 (71.4)	7 (70)
Female	7 (25)	0 (0.0)	2 (28.6)	3 (30)

$\chi 2 = 1.321$; $p = 0.724$

In our study DHEAS Level estimation was done in 44 patients. Normal value of DHEA in males is 10- 619 µg/dL and in females it is 12-535 µg/dL. Mean value of all 44 patients were 47.20±SD55.51. In males (32 cases) it was 50.369±51.2329, and in 12 females it was

38.778±SD67.4063 (Table- 4). In Males none of the patients had higher value while 4 (25%) male patient of Atherosclerosis, 4(80%) patients of Buerger's disease, 3(42.9%) patient of Thrombo embolism had Dehydroepiandrosterone level <10 µg/dL. 8(75%) male patient of Atherosclerosis, 1(20%) patient of Buerger's disease, 4(100%) patient of vasculitis and 4(57.1%). Thromboembolism had Dehydroepiandrosterone level between 10-619 µg/dL. Out of 12 females, 4(66.7%) female patient of Atherosclerosis, 1(33.3%) patient 0f Vasculitis, 3(100%) females of Thromboembolism had Dehydroepiandrosterone level <12 µg/dL. 2(33.3%) female patient of Atherosclerosis, 2(66.7%) patients of Vasculitis had Dehydroepiandrosterone level between12-535 µg/dL.

Table 4: Value of DHEAS Value of DHEAS in Female

DHEAS µg/dL	Diagnosis			
	Atherosclerosis (n=6)	Buerger's disease (n=0)	Vasculitis (n=3)	Thromboembolism (n=3)
	No. (%.)	No. (%.)	No. (%.)	No. (%.)
<12	4 66.7	0 0.0	1 33.3	3 100
12-535	2 33.3	0 0.0	2 66.7	0 0.0
>535	0 0.0	0 0.0	0 0.0	0 0.0

Value of DHEAS in Male

DHEAS µg/dL	Diagnosis			
	Artherosclerosis n=16	Buerger's disease n=5	Vasculitis n=4	Thromboembolism n=7
	No. (%)	No. (%)	No. (%)	No. (%)
<10	4 25	4 80.0	0 0.0	3 42.9
10- 619	12 75	1 20.0	4 100	4 57.1
>619	0 0.0	0 0.0	0 0.0	0 0.0

In the study Testosterone Level estimation was done in 50 patients. Normal value of Testosterone in male is 6.4-31.6 nmol/L and in females 0.2-4 nmol/L. Mean of all 50 patients were 8.18±SD6.31. Mean of all 38 Male cases was 9.425±6.483 and in 12 cases of Females it was 4.645±4.3021. Out of 38 male patients 4(19%) male patients of Atherosclerosis, all patients of Buerger's disease,3(60%) of Vasculitis, 3(42.9%) patient of Thromboembolism had serum Testosterone level <6.4nmol/L. 17(81%) male patients of Atherosclerosis, 2(40%) patients of Vasculitis, 4(57.1%) patients of Thromboembolic disease had Testosterone level 6.4-31.6nmol/L. Out of 12 Female patients 1 (50%) Female patient of Vasculitis, had Serum Testosterone level <0.2 nmol/L. 1(14.3%) female patient of Atherosclerosis, 1(50%) patient of Vasculitis, 3(100%) patient of Thromboembolic disease had Testosterone level 0.2-4.4nmol/L. 6(85.7%) female patient of Atherosclerosis, 100% had Testosterone level >4.4nmol/L.

Table 5: Value of Testosterone Male

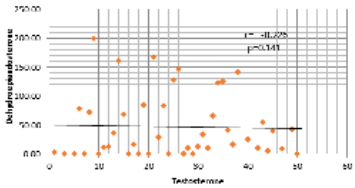
Testosterone nmol/L	Diagnosis			
	Atherosclerosis (n=21)	Buerger's disease (n=5)	Vasculitis (n=5)	Thromboembolism (n=7)
	No. (%.)	No. (%.)	No. (%.)	No. (%.)
<6.4	4 19.0	5 100.0	3 60.0	3 42.9
6.4-31.6	17 81.0	0 0.0	2 40.0	4 57.1
>31.6	0 0.0	0 0.0	0 0.0	0 0.0

Value of Testosterone in Female

Testosterone nmol/L	Diagnosis			
	Atherosclerosis (n=7)	Buerger's disease (n=0)	Vasculitis (n=2)	Thromboembolism (n=3)
	No. (%.)	No. (%.)	No. (%.)	No. (%.)
<0.2	0 0.0	0 0.0	1 50.0	0 0.0
0.2-4.4	1 14.3	0 0.0	1 50.0	3 100
>4.4	6 85.7	0 0.0	0 0.0	0 0.0

There is no significant correlation is noticed between Testosterone and Dehydroepiandrosterone in cases of PAD.

Graph-1 : Correlation of Serum Testosterone and DHEAS in PAD



Discussion

Our study shows that Peripheral arterial diseases were more common in males (76%) as compared to females (24%). Other studies show that the prevalent claudication is more common in men than in women, with male: female ratio ranging from 1.2 to 2.38 (Kennedy et al, 2005) (9). However, when ABI is used in PAD diagnosis, the overall prevalence is similar in both sexes, with a male: female ratio range of 0.8–1.2. The Multi-Ethnic Study of Atherosclerosis (MESA) found that although the prevalence of PAD defined by a low ABI was similar in both sexes, borderline ABI (0.9–0.99) was much more common in women than in men (10.6% vs. 4.3%) (McDermott et al, 2005) (10).

In our study most of the patients (36 out of 50 cases) were in the age group of 41-70 years. Other study shows a higher incidence of 1.6% per year was reported among men and women aged 55 to 74 years in the Edinburgh Artery Study (Leng GC, Lee AJ, 1996) (11). Another study shows Annual PAD prevalence among those aged 65 to 74 years ranged from 8.0% (95% CI 7.2–8.8%) to 9.0% (95% CI 8.0–10.0%) over the same time frame (Kalbaugh, 2017) (12). It also shows that 14% cases of peripheral arterial disease were of Less than 40 years of age. Other study shows Patients who develop PAD prior to the age of 45 (premature PAD) are more likely to have faster disease progression and worse outcomes, including limb loss and mortality (Pairolero et al, 1984; Levy et al, 1994) (13).

Our study shows 23.5% male cases of Atherosclerosis, 80% cases of Buerger's disease, 42.9 % cases of Thromboembolism had Dehydroepiandrosterone level <10 µg/dL. 76.5% male patient of Atherosclerosis, 20% patients of Buerger's disease, 100 % patient of Thromboembolism had Dehydroepiandrosterone level 10-619 µg/dL with Mean of (50.369±SD51.2329).

Our study shows 66.7% female cases of Atherosclerosis, 33.3 % cases of Vasculitis, 100% female cases of Thromboembolism had Dehydroepiandrosterone level <12 µg/dL. 33.3% female cases of Atherosclerosis, 66.7% cases of Vasculitis had Dehydroepiandrosterone level 12-535 µg/dL with Mean of (38.778±67.4063).

Our study shows 19% male cases of Atherosclerosis, 100% cases of Buerger's disease, 60% cases of Vasculitis, 42.9% cases of Thromboembolism had serum Testosterone level <6.4nmol/L. 81% male cases of Atherosclerosis, 40% cases of Vasculitis, 57.1% cases of Thromboembolic disease had Testosterone level 6.4-31.6nmol/L with Mean of (9.425±6.4836). Our study shows 50% Female cases of Vasculitis, had Serum Testosterone level <0.2 nmol/L. 14.3% female cases of Atherosclerosis, 50% cases of Vasculitis, 100% cases of Thromboembolic disease had Testosterone level 0.2-4.4nmol/L. 85.7% female cases of Atherosclerosis had Testosterone level >4.4nmol/L with Mean of (4.645±4.3021).

From the above mentioned values it is evident that in our study there is no significant correlation between serum Testosterone and DHEAS and Peripheral Arterial Disease (14-16). May be due to small sample size correlation between Testosterone and DHEAS and Peripheral Arterial Disease is not significant. However other study results showed that total serum Testosterone and DHEA-S were significantly decreased in PAD patients (Elod 2016). Another study had shown that

short term administration of testosterone induces a beneficial effect in men with peripheral artery disease and the effect may be related to direct peripheral artery-relaxing effects (Fowkes FG et al, 1997) (17). A study done by taking the subjects from Framingham heart study found that men with lower free testosterone had a significantly lower ankle-brachial index , similarly a higher free testosterone levels showed a protective effect on prevalent PAD in men (2011). A cross-sectional study revealed the observations of acute anti ischemic effect of testosterone in men with peripheral artery disease assessed using ankle brachial pressure index shows growing evidence that circulating testosterone is decreased in PAD patients (18-23). (Hans Jutberger et al 2007) (18).

Our study shows that there is no significant correlation between serum testosterone and Dehydroepiandosterone in Peripheral Arterial Diseas (r=-0.226, p=0.141). Other study shows that total serum testosterone levels are decreased in peripheral arterial disease (24-28). No significant changes of serum testosterone can be observed in advanced disease stages (Nagy Elod , Kun Imre Zoltan, Kelemen Piroska 2016) (29). Low serum testosterone and high serum estradiol associate with lower extremity peripheral arterial disease in elderly men. Other study shows Low levels of Endogenous Androgens Increase the Risk of Atherosclerosis in Elderly Men (The Rotterdam Study; Hak AE, Witteman, 2002) (30).

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