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Original Article

Physiology Section

Serum Vascular Endothelial Growth Factor and Aging: Study among Urban Population of Vijayapur, Karnataka, India

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ABSTRACT

Introduction: It is known that angiogenesis delays in aging. Vascular Endothelial Growth Factor (VEGF) is the most potent angiogenic factor. But the influence of aging on VEGF is still unclear among healthy population.

Aim: To determine the relationship between aging and VEGF among different age groups in both male and female subjects of Vijayapur city, Karnataka, India.

Materials and Methods: The present cross-sectional study conducted in Sri B.M. Patil Medical College (October 2016 to April 2017) on 196 healthy subjects male (n= 98) and female (n=98) subjects (20-95 years) were randomly selected among general population of Vijayapur city, Karnataka, India. Subjects were divided into six group: Group I (20-29 years), II (30-39 years), III (40-49 years), IV (50-59 years), V (60-69 years) and VI (>70 years). Anthropometric and physiological parameters like height (cms), weight (kg), Body Mass Index (BMI in kg/m^2), Body Surface Area (BSA in m^2), Pulse Rate (PR in bpm) and Blood Pressure (BP) were assessed. The VEGF was assessed by Enzyme-Linked Immunosorbent Assay (ELISA) method. Statistical analysis was done by using one-way ANOVA followed by post-hoc t-test and unpaired t-test by using SPSS software.

Results: Group I to Group VI showed significant ($p<0.001$) steady increase of VEGF in both male and female subjects. There was significant difference ($p<0.001$) of VEGF between male and female subjects.

Conclusion: Aging alters serum VEGF and causes vascular dysfunction. Females are greater protected against age related alteration of vascular pathophysiology due to greater VEGF concentration as compared to male counterparts.

Keywords: Angiogenesis, Body mass index, Vasculogenesis

INTRODUCTION

With aging, there is a progressive decline almost all physiological functions including vascular function [1]. Aging is an important risk factor for arterial aging and most forms of Cardiovascular Disease (CVD) [2]. Angiogenesis is not only an endogenous repair mechanism after ischaemic injury but also an essential adaptive response to physiological stress [3]. With aging, impaired angiogenesis and endothelial dysfunction likely contribute to the increased prevalence of CVD [3].

Angiogenesis acts as a major process in the development and maintenance of an individual health. Angiogenesis, the development of new vessels from pre-existing vasculature, is delayed in aging [4-8]. To proceed normally, the formation of new vessels requires endothelial cell activation, degradation of basement membrane, migration, and proliferation. These steps are regulated by interactions among cells, growth factors, and matrix proteins [9-11]. Growth factors, e.g., basic Fibroblast Growth Factor (b-FGF), VEGF, and Insulin-Like Growth Factor-1 (IGF-1), support the proliferation and migration of endothelial cells [12-17].

The VEGF is the most potent angiogenic factor. Matrix proteins, such as fibronectin, laminin, and Type 1 collagen provide the scaffold on which angiogenesis occurs [18-20]. In contrast, Secreted Protein Acidic and Rich in Cysteine; Osteonectin (SPARC), Thrombospondin-1 (TSP-1), and Thrombospondin-2 (TSP-2), are termed “matricellular” because they do not function as structural proteins but act as modulators of the angiogenic response [21-25]. The local balance among these competing factors is critical in determining if blood vessels will develop within a tissue or not.

For ischaemic diseases, induction of angiogenesis acts as a promising therapeutic approach [3]. Although, much is known about angiogenesis in general, the changes that occur during angiogenesis with aging are not well defined. So, to understand and manage CVD it is important to understand the basis of age related impairment of endothelial function and angiogenesis. So, the present study was undertaken to know the influence of ageing on VEGF among the healthy general population of Vijayapur, Karnataka, India.

MATERIALS AND METHODS

The present cross-sectional study was started after approved by the Institutional Ethical Committee (IEC Ref No-141/2015-16 dated July 20, 2015) Sri B.M. Patil Medical College, Hospital and Research Centre, (BLDE Deemed to be University) as per the ICMR guidelines 2006. Screenings were performed from October 2016 to April 2017 and included 192 apparently healthy subjects of age ranging from 20-95 years from Vijayapur city, Karnataka, India. Informed consent was obtained for participation in the study. Subjects from both sexes with resting BP <140/90 mmHg, BMI <30 kg/m^2 and subjects not taking medications or dietary supplements were included. Subjects with alcohol intake, smoking, tobacco consumption in any form, suffering from mental disorders, hypercholesterolemia, hypertension, diabetes mellitus and taking medications like statins, antidiabetics, diuretics, antihypertensives, beta blockers, vasodilators etc., were excluded from the study. All the recordings were done in the morning between 9-11 am at room temperature following supine rest for 10 minutes.

Anthropometric parameters like height in centimetres (cms), weight in kilograms (kg), BMI in kilograms per square meter (kg/m^2) and BSA in square meter (m^2) and physiological parameters like pulse rate in (beats/minute), Systolic Blood Pressure (SBP) in millimetre of mercury (mmHg), Diastolic Blood Pressure (DBP) (mmHg), Pulse

Pressure (PP) (mmHg) and Mean Arterial Pressure (MAP) (mmHg) were recorded by using standard procedures. Total serum VEGF was measured as an index of endothelial function. Serum VEGF was estimated based on the principle of a solid phase ELISA by using a commercially available kit [26].

Sample Size Calculation

We screened 210 subjects, among them 192 subjects were included in the study. A total of 96 male subjects and 96 female subjects were sufficient to detect a clinically important difference of 0.8 between groups in detecting change assuming a standard deviation of 2 using a two tailed z-test of means between groups with 80% power and a 5% level of significance.

The entire sample was divided into six groups by age decades including male and female together

- Group I: between 20 and 29 years (n=32)
- Group II: between 30 and 39 years (n=32)
- Group III: between 40 and 49 years (n=32)
- Group IV: between 50 and 59 years (n=32)
- Group V: between 60 and 69 years (n=32)
- Group VI: 70 plus years (n=32)

STATISTICAL ANALYSIS

Data was expressed as mean±Standard Deviation (mean±SD). The data have been expressed in the form of tables and graphs. Differences between mean values of parameters between Group I, Group II, Group III, Group IV, Group V and Group VI were evaluated by one-way ANOVA followed by Post-hoc test (Least significant difference). We compared mean values for male and female in each age group using the unpaired t-test. Correlation of VEGF with age was done by Pearson's correlation. The level of statistical significance was observed at $p<0.05$, $p<0.01$ using SPSS software 16.0.

RESULTS

The anthropometric and physiological characteristics among males divided into six groups by age [Table/Fig-1]. There were no significant difference in weight, height, BMI, BSA, PP and MAP between the observed groups. In case of PR ($p<0.05$) ANOVA showed significant results. The anthropometric and physiological characteristics among female subjects divided into six groups by age decades [Table/Fig-2]. In case of height ($p<0.01$), weight ($p<0.001$), BMI ($p<0.01$), BSA ($p<0.01$), PR ($p<0.01$), PP ($p<0.001$), and MAP ($p<0.01$), ANOVA shows significance.

The serum VEGF between male and female subjects in all the six age matched groups [Table/Fig-3]. Results from unpaired t-test showed significant difference ($p<0.001$) between male and female subjects in all the age groups. Results reflect that there was a steady increase of VEGF in both male and female as age progressed. Interestingly VEGF concentration in female, in all the age matched groups with male was found to remain significantly higher.

Parameters	Age groups (years)							
	Group I	Group II	Group III	Group IV	Group V	Group VI	ANOVA	
	20-29 years (n=16) (mean±SD)	30-39 years (n=16) (mean±SD)	40-49 years (n=16) (mean±SD)	50-59 years (n=16) (mean±SD)	60-69 years (n=16) (mean±SD)	70 years plus (n=16) (mean±SD)	f-value	p-value
Weight (Kg)	66.2±8.5	65.5±4.64	71.7±9.2	64.9±4.1	66±4.87	59.44±9.6	2.010	0.089
Height (cm)	167.5±4.0	167.7±4.2	161.55±5.34	166.7±7.66	167.0±5.5	161.9±6.0	2.085	0.081
BMI (kg/m^2)	24.0±2.8	23.3±1.2	25.8±2.5	24.8±0.9	23.9±4.54	21.9±2.3	2.130	0.080
BSA (m^2)	1.76±0.12	1.75±0.74	1.84±0.14	1.72±0.2	1.80±0.16	1.63±0.15	1.868	0.127
PR (bpm)	73.6±8.43^{I,VI}	74.9±9.92^{VI}	77.8±9.60^{VI}	75.5±6.81^{VI}	73.0±10.66^{VI}	63.0±7.39^{I,II,III,IV,V}	2.978	0.026
PP (mmHg)	56.31±5.4	56.39±6.28	47.59±3.69	47.79±6.81	57.42±6.8	57.67±7.7	2.028	0.101
MAP (mmHg)	87.39±6.79	88.89±5.21	88.42±4.69	94.69±5.39	100.9±8.69	101.9±7.79	1.489	0.222

[Table/Fig-1]: Anthropometric and physiological characteristics of male subjects.
Data are Mean+SD. Values in the final column represent results of one-way analysis (ANOVA) among different age groups. Post-hoc comparisons were made between each group with LSD method. Superscripts I, II, III, IV, V and VI on each of the group are significantly differ from that group at p<0.05 level. BMI: Body mass index, BSA: Body surface area, PR: Pulse rate, PP: Pulse pressure, MAP: Mean arterial pressure

Parameters	Age groups (years)							
	Group I	Group II	Group III	Group IV	Group V	Group VI	ANOVA	
	20-29 years (n=16) (mean±SD)	30-39 years (n=16) (mean±SD)	40-49 years (n=16) (mean±SD)	50-59 years (n=16) (mean±SD)	60-69 years (n=16) (mean±SD)	70 years plus (n=16) (mean±SD)	f-value	p-value
Weight (Kg)	56.1±8.59^{VI}	55.79±6.69^{VI}	59.19±6^{VI}	61.9±7.0^{VI}	56.9±9.39^{VI}	44.1±4.9^{I,II,III,IV,V}	3.430	0.008
Height (cm)	158.31±2.69	151.9±6.29	151.2±3.49	157.1±3.89	150.10±4.81	149.1±3.92	8.130	0
BMI (kg/m^2)	22.39±3.49	24.10±2.90	25.40±2.28	25.01±2.56	25.43±3.41	19.81±2.41	4.030	0.003
BSA (m^2)	1.60±0.10^{VI}	1.50±0.10^{VI}	1.60±0.08^{VI}	1.63±0.09^{VI}	1.52±0.16^{VI}	1.32±0.1^{I,II,III,IV,V}	3.560	0.009
PR (bpm)	73.9±8.8	74.2±10.9	72.1±8.1	75.4±5.0	71.91±8.5	65.31±9.21	2.310	0.030
PP (mmHg)	44.4±7.9^{V,VI}	44.6±3.67^{V,VI}	46.71±5.2^{V,VI}	48.4±5.5^{V,VI}	64.39±12.78^{I,II,III,IV}	64.32±9.9^{I,II,III,IV}	7.350	0
MAP (mmHg)	82.50±6.8^{V,VI}	85.2±8.5V,VI	88.1±7.89	91.89±5.38	95.7±8.69^{I,II}	101.36±17.74^{I,II}	3.267	0.012

[Table/Fig-2]: Anthropometric and physiological characteristics among female subjects.
Data are Mean+S.D. Values in the final column represent results of one-way analysis (ANOVA) among different age groups. Post-hoc comparisons were made between each group with LSD method. Superscripts I, II, III, IV, V and VI on each of the group are significantly differ from that group at p<0.05 level. BMI: Body mass index, BSA: Body surface area, PP: Pulse pressure, MAP: Mean arterial pressure

VEGF in pg/mL					
Age groups	Age in years	Male subjects (mean±SD)	Female subjects (mean±SD)	Unpaired t-test	
				t-value	p-value
Group I	20-29 years (n=16)	277.8±30.06	429.78±26.17	-14.758	≤0.001
Group II	30-39 years (n=16)	328.4±31.75	555.43±32.50	-19.349	≤0.001
Group III	40-49 years (n=16)	415.68±66.91	597.64±19.67	-10.105	≤0.001
Group IV	50-59 years (n=16)	430±56.81	648.92±21.55	-13.953	≤0.001
Group V	60-69 years (n=16)	485.73±14.56	675.74±29.55	-22.332	≤0.001
Group VI	70 years plus (n=16)	626.6±46.06	722.19±74.81	-4.214	≤0.001

[Table/Fig-3]: VEGF in pg/mL among both male and female subjects.
Data are Mean±SD. Values in the final column represent results of unpaired t-test between male and female subjects. p<0.05, considered as statistically significant

The ANOVA for all six groups in males which found to be statistically significant (p-value=0.001) [Table/Fig-4]. Similarly, significant difference in female subjects in all the age groups by ANOVA [Table/Fig-5].

ANOVA					
VEGF in pg/mL in male subjects					
	Sum of squares	Degrees of freedom	Mean square	f-value	p-value
Between groups	1130701.206	5	226140.24	113.528	0.031597
Within groups	167322.187	90	1991.931		
Total	1298023.394	95			

[Table/Fig-4]: VEGF in pg/mL in male subjects.
Values in the final column represent results of ANOVA between group I, II, III, IV, V and VI of male subjects. p<0.05, considered as statistically significant

ANOVA					
VEGF in pg/mL in female subjects					
	Sum of squares	Degrees of freedom	Mean square	f-value	p-value
Between groups	808190.837	5	161638.167	106.995	0.036093
Within groups	126899.951	90	1510.714		
Total	935090.788	95			

[Table/Fig-5]: VEGF in pg/mL in female subjects.
Values in the final column represent results of ANOVA between group I, II, III, IV, V and VI of female subjects. p<0.05, considered as statistically significant

DISCUSSION

Angiogenesis is fundamental for many physiological and pathological processes. In the present study, we assessed VEGF in relation to ageing in apparently healthy males and females among different age groups (20-95 years).

The present study showed a statistically significant (p<0.05) decrease in PR after the age of 70 years i.e., in Group VI (70 plus years) in both male and female subjects. The present study also showed significant increase (p<0.001) in PP after the age of 60 years in females i.e., in Group V (60-69 years) and VI (70 plus years). A linear rise in SBP from age 30-84 years with initial increase in DBP were reported earlier by Franklin SS et al., [27]. The study further reported a decline of DBP after the age of 50 years with concomitant increase of PP and MAP [27]. The present results from BP in all the age groups in female subjects corroborate with the study of Franklin SS et al., [27].

The present results showed an increase in VEGF as age increases in both male and female subjects where as in case of females the concentration of VEGF remained consistently higher in all the age groups (20-70 plus years) as compared to their male counterparts. The results indicate a greater angiogenesis in females in all the age groups which may be considered as greater protection against vascular aging due to VEGF induced angiogenesis [Table/Fig-3]. The present results corroborated with study by Malamitsi-Puchner A et al., [28]. Impaired angiogenesis with reduced VEGF expression is found to be associated with aging [29]. Higher VEGF expression in aging may also be due to greater expression of oxygen sensing gene HIF-1α to combat age associated alteration of VEGF expression [30]. The relationship between distinct ocular aging and VEGF is well established [31]. Age related altered angiogenesis indicates endothelial dysfunction which may even lead to cerebral death [14,32]. Angiogenesis in aging is not merely delayed, but is altered due to multiple factors like altered inflammatory response, reduced expression of proangiogenic factors, decreased vessel density, less newly deposited collagen, and increased expression of TSP-2, an inhibitor of angiogenesis. The expression of VEGF was decreased in sponges from the mice aged at 14 days and 19 days compared to young tissue at the same time points which indicated an impaired angiogenesis [33]. The same study also observed a moderate increase in VEGF expression in aged tissue from 14-19 days [33]. Hence, results from the present study clearly indicate age associated greater vascular stability in female as compared to male counterparts. Decreased VEGF secretion among male subjects in all the age groups as compared to females clearly indicate lower angiogenesis or there may be possibly greater impairment of oxygen sensing mechanism in vascular system which leads to vascular integrity.

Some studies have demonstrated that administration of angiogenic growth factors as in recombinant protein therapy or gene transfer may facilitate angiogenesis in animal models of myocardial and limb ischaemia [34,35]. Such therapeutic strategies in older patients may help to manage the CVD due to impaired angiogenesis with aging.

LIMITATION

We could not evaluate serum VEGF expression by Western blotting. Further studies are needed to assess oxygen sensing protein like HIF 1α and VEGF expression by Western blotting.

CONCLUSION

Aging alters serum VEGF and causes vascular dysfunction. Higher serum VEGF levels with aging both in females and males indicates increased rates of angiogenesis. Females have an augmented protection against age related alteration of vascular pathophysiology due to greater VEGF concentration as compared to their male counterparts.

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