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Assessment of Vascular Age in Asymptomatic Persons in Indian Population

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Original Research Article

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Abstract: The Concept of vascular age (Age of arteries) is a concept related to cardiovascular risk that might be more easily understood by all patients. This study aimed to evaluate whether vascular age is advanced as matched to their chronological age in apparently healthy, asymptomatic population and to assess the contributing risk factors for premature vascular ageing. Hospital based, observational study of 547 individuals conducted from May 2015 to December 2017. Persons enrolled were asymptomatic with normal ECG, chest X-RAY and ECHO and were drug free. Population enrolled were monitored by regular visit and telephonically for the events. The vascular age of the population was calculated using Framingham vascular age calculator. Statistical analyses were done using SPSS software V 20.0. The cut off value of $P < 0.05$ was considered statistically significant. RESULTS**:** The mean chronological age of the study population was 53.92+/- 14.86 years whereas mean vascular age was 63.55+/- 15.51 years, and the difference 9.87+/-11.05 between both was statistically significant ($P < 0.001$). Contributory risk factors for advanced vascular age apart from chronological age were smoking, diabetes, Low HDL, Total cholesterol/HDL ratio and systolic blood pressure. Results of regression analysis showed that vascular age progression was highly associated with, Age 1.059 (C.I 1.016 to 1.105) P=0.007, SBP 1.045 (C.I 1.018 to 1.072), P=0.001, Smoking 2.657(C.I 1.177to6.000) p=0.019, Diabetes mellitus.1.84 (CI 0.876 to0.958) p= 0.05 and Triglyceride 1.010(1.004to1.016) p=.001.CONCLUSIONS: Significant difference was observed between chronological and vascular age, so routine screening for vascular age and risk factors (specially lipid profile and blood pressure measurement) is strongly advocated for asymptomatic relatives of patients with IHD.

Keywords: Vascular age, cardiovascular diseases, Indian population.

INTRODUCTION

Cardiovascular diseases (CVD) including coronary artery disease (CAD) and stroke, are leading cause of mortality and morbidity in the developing countries of the world [1]. The origin of emerging CVD risks in Indians lies in epidemic transition which is a result of affluence, urbanization and mechanization [2]. The concept of vascular age was developed by public health experts who work on the venerable Framingham Heart Study as a way to help regular folks to understand their risk of having a heart attack, stroke, chest pain, peripheral artery disease or another heart-related condition, including death. A clinical trial in Europe found that people who were told their heart age improved their heart health more than people who were not told their absolute risk of developing cardiovascular disease. In that trial, those who learned their heart age were able to reduce it by 1.5 years over the course of a year, compared with a reduction of only 0.3 years for those who got the traditional risk information.

Before going to introduce the vascular age ,it is necessary to define the cardiovascular disease, so as per the Framingham Heart Study, CVD defined as a composite of CHD (coronary death, myocardial infarction, coronary insufficiency, and angina), cerebrovascular events (including ischemic stroke, haemorrhagic stroke, and transient ischemic attack), peripheral artery disease (intermittent claudication), and heart failure. In case of CAD, the unique phenotypic profile of Asians differentiates them from other populations which suggest possible involvement of ethnicity based causative factors [3]. Prognosis and prediction of coronary heart disease (CHD) and other cardiovascular events are complex processes involving the study of interactions between genetic and environmental factors over an extended period of time. One of the most accepted models for CHD risk

prediction was proposed and developed by Framingham investigators in 1998[4]. The original study was a community based study of 5209 white subjects selected from a suburb west of Boston. In spite of this, the accuracy of Framingham equation in predicting the CHD risk in culturally diverse population is fairly high and uniform due to its systematic validation in various populations [5, 6].

AIM

The present study is aimed to establish a single multivariable risk function (the vascular age) that predicts risk of developing all CVD and of its constituents and calculation of vascular age and difference of vascular age and chronological age in Indian population.

Although called heart age for simplicity of risk communication in primary care, the heart age really reflects vascular age.

MATERIALS AND METHODS

Design and data collection: This cross-sectional and randomized screening study was conducted at post graduate department of Cardiology, Jawahar Lal Nehru Medical College, Ajmer, Rajasthan, after obtaining approval and clearance from the institutional ethics committee. All participants were provided written informed consent, and the study protocol was approved by the Institutional Review Board at JLNMC, Ajmer.

The study sample consisted of total 547 individuals (359 males and 188 females), who were apparently healthy, asymptomatic from 18 to 74 years of age non missing data on covariates in the study.

The subjects taking any medications and with abnormal stress test were excluded from the investigation. All patients had normal baseline electrocardiography and 2D echocardiography. The details of demographic data, ethnicity, family history of CAD and smoking were collected for each individual. Subjects were advised to fast at least for 12 h before blood investigations. Total cholesterol, triglycerides, total lipid, lipoproteins–low density lipoproteins, high density lipoprotein, and very low density lipoprotein and glucose concentrations were measured by International Federation of Clinical Chemistry approved enzymatic methods using commercially available kit on auto analyser (ARCHITECH PLUS ci4100, Germany). Lipids levels were classified according to the recommendations of National Cholesterol Education Program and Adult Treatment Panel III guidelines. Diabetes was defined as fasting glucose 126 mg/dl. or use of insulin or oral hypoglycaemic medications. Antihypertensive medication use was ascertained by the physician examiner at the heart study and based on self-report.

Blood pressure of the population was measured as per the earlier reported guidelines and hypertension was diagnosed if the systolic blood pressure was higher than 140 mmHg or the diastolic blood pressure was above 90 mm Hg[7].

Measurement of CVD Risk Factors

At each heart study examination, participants underwent a physical examination, anthropometry, blood pressure determination, and blood investigations for vascular risk factors. Blood pressure measurements were made on the left arm of the seated participants with a mercury-column sphygmomanometer and an appropriately sized cuff; the average of 2 physician-obtained measures constituted the examination blood pressure. Detailed descriptions of the examination procedures and criteria for CVD events also have been reported [8].

Calculation of vascular age was made by point scoring system as fully described and statistically confirmed by D'Agostino *et al*. and all the relevant tables which were used as base line in calculations are given in original article [10].

Multivariable Models and Estimation of General CVD Risk Functions

Original work of D"Agostino, published in circulation 2008, was used as baseline for the statical validation [10]. We used sex-specific Cox proportional-hazards regressions [9] to relate risk factors to the incidence of a first CVD event during a maximum follow-up period of 2.5 years after confirming that the assumption of proportionality of hazards was met. From these models, we estimated mathematical CVD risk functions [9] referred to as a general CVD risk function; these functions were used to estimate 10-year absolute CVD risk. Covariants included in Cox models were age, total cholesterol, HDL cholesterol, systolic blood pressure, antihypertensive medication use, current smoking, and diabetes status. Other variables such as diastolic blood pressure, body mass index, and triglycerides also were considered, but they were not statistically significant. All the continuous variables were naturally logarithmically transformed to improve discrimination and calibration of the models and to minimize the influence of extreme observations.

STATISTICAL ANALYSIS

The statistical calculations were performed using SPSS software v 20.0 (Chicago, IL, USA) Quantitative data was expressed as mean SD whereas qualitative data was expressed as percentage. Univariate analysis of the continuous data was performed using student's t-test, whereas chi-square test was used for the categorical data. One-way analysis of variance (ANOVA) was applied to compare the results of three cohorts. The cut off value of $P < 0.05$ was considered for the statistical significance. Linear regression model was applied to the data to measure the strength of

particular risk factors in predicting premature vascular ageing.

RESULTS

Total 650 patients were included in study but latter on during the follow up of period of 2.5 years , 103 person lost due to inability to reach hospital (figure 1) Total 547 subjects were considered for final statistical analysis, the mean chronological age of the population was 53.92+/- 14.86 years whereas mean vascular age was 63.55+/-15.51 years. The vascular age was significantly higher than the chronological age with discrete value of 9.87+/- 11.05 years (table 1).

Table-1: General characteristics of study population

Number (%)	Mean ±SD(Min to Max)	
n=547		
Chronological age	53.92 ±1 4.86(19 to 95)	
Vascular age	63.55 ± 15.51(28 to 99)	
Difference	9.87 ± 11.053 (-20 to 43)	
Cholesterol	159.94 ± 50.254 (47 to 375)	
High density lipoprotein (HDL)	35.23 ± 15.08 (8 to 141)	
Males	359(65.63)	
Female	188 (34.37)	
Total cholesterol/high density	5.22 ± 2.57 (0.6 to 18.6)	
SBP	125.82 ± 15.33 (82 to 170)	
SMOKING	272(49.73)	
TYPE 2 DM	148 (27.06)	
Disease		
ANGINA	1	0.18
CSA	5	0.91
CVA	2	0.37
MI	14	2.56
PVD	5	0.91
UA	4	0.73
dvd	1	0.18
dvd//lad	1	0.18
dvd/lad/lcx	1	0.18
dvd/lad/rca	1	0.18
dvd/lcx80/r	1	0.18
lad	1	0.18
normal	1	0.18
tvd	3	0.55

On follow up, we found that no of persons who developed disease were 31. Among total, coronary artery disease developed in 24 patients, cerebrovascular events developed in 2 persons and peripheral vascular disease developed in 5 persons.

Among the total 24 patients of the coronary artery disease, total 10 patients went for coronary angiography in which 5 patients revealed DVD ,1 patient of SVD, 1 patient normal coronary artery ,and 3 person TVD.

Table-2: Correlations of covarients

Correlations										
		Age	HDL	TC	Ratio	SBP	Vascular Age	Subtract	TG	CV Risk %
Vascular Age	Pearson Correlation	.718**	-.151**	.021	.136**	.340**	1	.409**	.041	.567**
	Sig. (2-tailed)	.000	.000	.620	.001	.000		.000	.334	.000
	N	547	547	547	547	547	547	545	547	547
CV Risk %	Pearson Correlation	.378**	-.144**	-.029	.172**	.231**	.567**	.258**	-.008	1
	Sig. (2-tailed)	.000	.001	.500	.000	.000	.000	.000	.847	
	N	547	547	547	547	547	547	545	547	547
*. Correlation is significant at the 0.05 level (2-tailed).										
**. Correlation is significant at the 0.01 level (2-tailed).										

Study of covariants for vascular age was done individually. The mean value of different covariates is such as total cholesterol 159.94 mg/dl, high density cholesterol 35.23 mg/dl, Total cholesterol /high density cholesterol was 5.22.

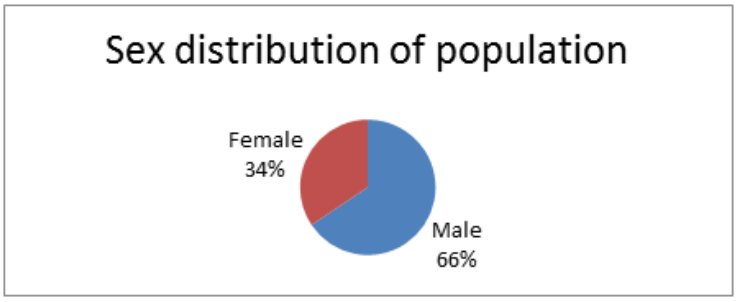

Fig-1: Sex distribution of population

The study population was categorized into three cohorts based on their age (figure 2)

Cohort I: Vascular age lesser than the chronological age (97)
Cohort II: Vascular age equal to the chronological age (36)
Cohort III: Vascular age greater than the chronological age (414)

Smokers in study were 272 (49.73%) and Diabetics 148 (27%).

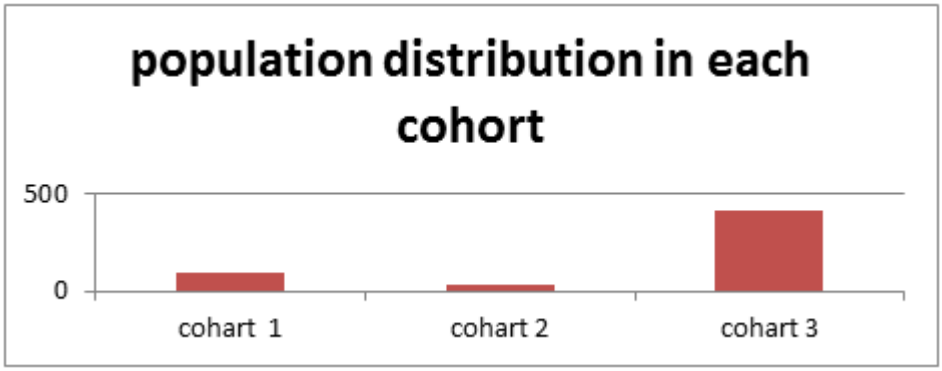

Fig-2: Population distribution in each cohort

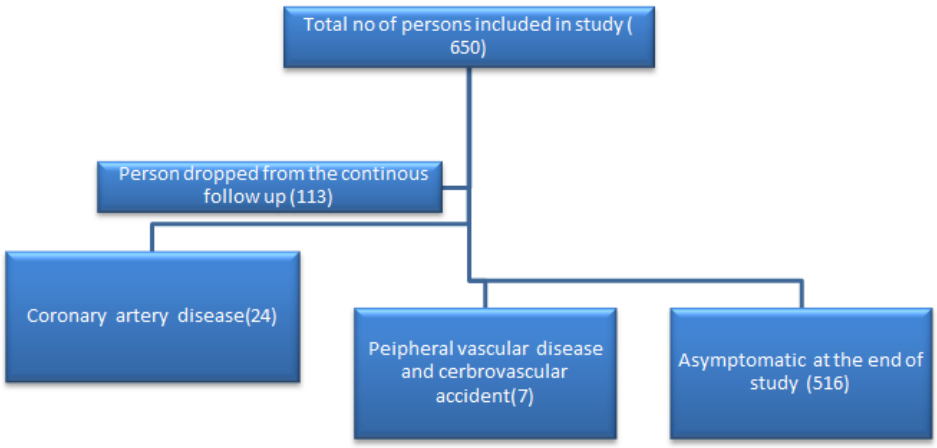

Fig-3: Distribution of events in study

Follow-Up and Outcome Events

After study the correlations table, we found that vascular age are strongly associated with the age (r=0.718), whereas the other two co-variants like systolic blood pressure and the difference of chronological and vascular age are moderately

correlated with the vascular age(r=0.340 and r=0.409 respectively). High density cholesterol has low negative correlation with the vascular age unlike the ratio of total cholesterol and high density cholesterol has low positive correlation. So far as, vascular age has their association with the risk factor,the cardiovascular risk percentage is also separately related with the different co-variants individually .Vascular age(r=0.567) has highest and strongest positive correlation with the cardiovascular risk whereas chronological age(r=0.378) is moderately correlated with the CV risk .High density cholesterol (r= -0.144) has low negative correlation with the CV risk. By concluding, both vascular age and CV risk are negatively correlated with the high density lipoprotein (HDL). One thing, to be highlighted that chronological age itself is the significant covariant which is strongly associated for the vascular age. Other remarkable point, observed is that total cholesterol has weak correlation with the vascular age as well as with the cardiovascular risk.

Table-3: Distribution and comparison trends of various risk factors according to vascular age deviations

	Cohart1 (N=97)		Cohart 2(N=36)		Cohart 3 (N=414)		P value LS
	mean ±SD		mean ±SD		mean ±SD		
Chronological Age	60.33	14.96	57.67	17.7	52.09	14.108	<0.001S
Age Group							
less40	8	8.25	6	16.67	94	22.71	0.005S
more40	89	91.75	30	83.33	320	77.29	
Vascular Age	54.31	13.79	57.67	17.73	66.22	14.73	<0.001S
Difference	-4.65	6.04	0	0	14.16	8.75	<0.001S
sex							
M	59	60.82	26	72.22	274	66.18	0.46NS
F	38	39.18	10	27.78	140	33.82	
Smoking	31	31.96	10	27.78	231	55.80	<0.001S
DM	23	23.71	10	27.78	115	27.78	0.71NS
HDL	45.49	18.04	34.17	8.55	32.92	13.75	<0.001S
TC	159.36	37.86	159.58	58.53	160.67	51.63	.969
TC/HDL	3.99	1.90	4.794	1.69	5.55	2.68	<0.001S
SBP	118.41	11.33	124.00	14.56	127.71	15.68	<0.001S

As per table 3, A total of 547 persons were included in the study who covered the whole observation period, categorised in three cohorts as described in methods. Cohort 1 contained total 97 persons of which vascular age of 54.31 years was the lower than the chronological age 60.33years. Cohort I was made up of 59 males with 38 females.The covariate like smoking,lower HDL,total cholesterol /HDL ratio and systolic blood pressor was statically significant for calculation of vascular age. The cohort 2 which comprises of toal 26 males and10 females has equal chronological and vascular age. But remarkebly cohort 3 ,which was largest cohort of 414 persons, has 274 males and 140 females had chronological age of mean 52.09 years .The vascular age calculated was 66.22 years. The difference of both the vascular and chronological age was 14.16 years .The contributing factor for higher vascular age were smoking , lesser mean HDL ,and relatively higher mean systolic blood pressor .These covariants were statistcally significant with p value <0.05.

Table-4: Multivariate regression Analysis

		95% C.I.for EXP(B)		
	Exp(B)	Lower	Upper	Sig.
Sex	1.772	.781	4.021	.171NS
Age	1.059	1.016	1.105	.007S
HDL	1.002	.966	1.040	.912NS
TC	1.002	.992	1.012	.761NS
RATio	1.073	.857	1.343	.539NS
SBP	1.045	1.018	1.072	.001S
Smoking	2.657	1.177	6.000	.019S
dm	2.184	.975	4.893	.05S
Vascular Age	.916	.876	.958	<0.001S
TG	1.010	1.004	1.016	0.001S
Constant	.000			.000

On multivariate analysis, Variables like Age, Sex, Smoking, DM, SBP, total HDL, Total Cholesterol, Vascular age, Triglyceride and TC/HDL ratio were taken as covariants. 0n analysis, Age 1.059(C.I 1.016 to 1.105) P=0.007, SBP 1.045 (C.I 1.018 to 1.072), P=0.001, Smoking 2.657(C.I 1.177 to 6.000) p=0.019, Diabetes Mellitus .184(CI 0.876 to0.958) P=0.05and Triglyceride 1.010(1.004to1.016) p=0.001 were observed significant risk predictors in predicting premature vascular ageing or events occurred.

DISCUSSION

To the best of our knowledge, this is the first ever large observational study designed to assess individuals for increased vascular age in Indian cohort. This work also provides some of the most relevant findings regarding the factors involved in advanced vascular age in apparently healthy and asymptomatic Indians. Surprisingly, we found that only 17.73.% of the population was having vascular age lesser than their chronological age, where as 75.68% of the population was suffering from premature vascular ageing making them susceptible for occurrence of CVD.

D'Agostino *et al*. had developed a simple algorithm involving classical risk factors of CHD such age, lipids, systolic blood pressure, treatment for hypertension, smoking and diabetes to quantify a multivariable risk of CHD in the form of vascular age[10]. This study's obesrvations concluded that by itself chronological age is strongest contributor for the vascular age in indians along with the systolic blood pressure and difference of vascular and chronological age which are moderately strong.

Although dyslipidemia is well established trigger for various cardiovascular risk disorders ,in our study we have found lesser significance of it than the chronological age itself [11]. One of the first land mark finding of Framingham study was the establishment of relationship between TC and CHD risk.

Nowadays, the 'cholesterol centric' approach to CVD is an obsolete concept as the high levels of LDL, elevated TG, TL, VLDLs and low levels of HDL are also known to contribute vascular age progression which was later updated by Framingham investigators also but our study offer is slight lesser support for this hypothesis.

The lifetime risk of CVD is substantial[12] and the condition is often silent or may strike without warning, underscoring the importance of prevention. Investigators have identified key risk factors that account for most CVD burden in the community, and numerous reports have demonstrated the clustering and conjoint influences of multiple risk factors in mediating disease vascular risk[2,4,6,7].

But this study establishes systolic blood pressure as one of the strongest predictor of advanced vascular age showing higher frequencies in male when compared with female which is in accordance with earlier reported studies[15].

This is in contrast to one indian study, that found indians females (61.4%) are more likely to be hypertensive than males (55.2%). This remarkable loss of the estrogen protective effect in indian females could be partially explained by less effective baroreflex buffering of blood pressure in women than men and presence of associated comorbidities[16]. Centripetal obesity, as defined by WC is a prime indicator of disturbed lipid metabolism and is an independent risk factor of atherosclerosis[17].

Although not incorporated in Framingham equation as well in our study, the IDEA study presented that visceral obesity is linearly related to the incidence of CAD regardless of BMI[18] we also have not included it in our study ,it is also a limitation of our study.

Diabeties mellitus is not apperaing as significant factor for calculation of vascular age, initialy in simple evaluation of data, this may be due to use of point scoring system for calculation of vascular age rather continous scoring system.

We included only six covariants for assesment of vascular age ,if we had included carotid intima thickness ,it would be better and more physiological.

Other point of discussion is, lesser no of females in study compared to male, that happened because we enrolled only the patient's attendent acompanying them, so being remote area only few females gave cosent to be enrolled and we also had lesser no of female attendents along with patients.

In our study, 77.29% of the population affected with advanced vascular age were having chronological age above 40 years also establishing the fact that age itself is the strongest covarient for vascular age.

Our results clearly states that the gap between vascular age and chronological age gets widened as people grow older due to greater expression of framingham equation risk factors.

CONCLUSION

The present study presents a sex-specific multivariable risk factor algorithm that can be conveniently used to assess general CVD risk and risk of individual CVD events (coronary, cerebrovascular, and peripheral artery disease and heart failure). The estimated absolute CVD event rates predicted can be used to quantify risk and to guide preventive primary

care. We utilised this vascular age calculation for the indian asymptomatic people, and got the conclusion like mentioned below.

- Indians are 'older' for their vascular age by mean 9.87 years when compared with their chronological age.
- The risk factors contributing to the advanced vascular age for Indians are dyslipidemia, hypertension , Diabetes and smoking apart from chronological ageing and male gender.
- Diabetes and smoking showed satisfactory influence as proved by multivariate regression analysis in the study group and this could be partly explained by the fact that distribution of CVD risk factors are highly prone to ethnic and genetic variation making some population more susceptible to certain diseases.
- These finding may explain earlier occurrence of CVD in Asian Indians approximately by a decade than Caucasian population. In the light of our findings, routine screening for advanced vascular age and potential 'at risk population' in asymptomatic patients is strongly advocated.

Strengths and Limitations of study

The large community-based sample that is under continuous surveillance using the same standardized criteria for CVD incidence and the assessment of model performance measures such as discrimination, calibration, and exchangeability with disease-specific profiles strengthen the present investigational study.

However, several limitations of the present study must be acknowledged.

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