Original Article

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Arterial Stiffness and Trace Elements in Apparently Healthy Population- A Cross-sectional Study

Community Medicine Section

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ABSTRACT

Introduction: Stiffening of arteries is a natural ageing process. Any diseases/disorders or risk factors that escalate oxidative stress, microvascular inflammation and endothelial damage may promote to premature vascular stiffening. Any imbalance in these trace element levels may independently contribute to the changes in the components in the arterial wall and thus, arterial stiffness via one or more mechanisms.

Aim: To evaluate the severity of arterial stiffness in apparently healthy population and also to evaluate role of various risk factors and trace elements in the severity of arterial stiffness

Materials and Methods: Male and female subjects living in urban and rural areas of Nellore district, Andhra Pradesh, India, between 20-60 years, apparently normal as judged by the clinician basing on clinical and laboratory findings, were studied. Carotid-Femoral Pulse Wave Velocity (cf-PWV) a marker of arterial stiffness was assessed using non-invasive blood pressure curve monitoring (periscope). Furthermore, we also estimated serum levels of Copper (Cu), Zinc (Zn), Selenium (Se), chromium (Cr), Aluminium (Al), silicon (Si), Manganese (Mn), Molybdenum (Mb), Vanadium (Vn) and lead (Pb) using atomic absorption spectrophotometer. ANOVA and Chi-Square test were used to study the clinical correlations between severity of arterial stiffness, risk factors and trace elements.

Results: A total of 737 apparently healthy subjects participated in this cross-sectional study. Of the total 542 (73.5%) were from rural and the remaining 195 (26.5%) were living in urban areas, 328 (44.5%) were males, and 409 (55.5%) were females.

A 63.5% (468/737) had normal arterial stiffness followed by 14.5% (107/737) with mild stiffness, 7% (57/737) had moderate stiffness and 14.2% (105/737) had severe arterial stiffness. Smoking, alcohol, blood pressures, fasting blood sugar, and total cholesterol, Cu, Al and Vn correlated ($p<0.05$) with different grades of arterial stiffness.

Conclusion: A 36.5% had high arterial stiffness despite being apparently healthy. Smoking, alcohol, blood pressures, fasting blood sugars, and total cholesterol, Cu, Al and Vn could have contributed for such an abnormality. Caution has to be executed while understanding the study results since the pathophysiological process is complex.

Keywords: Aortic stiffness, Cardiovascular risk factors, Carotid-femoral pulse wave velocity

INTRODUCTION

Aortic or cf-PWV, a marker of arterial stiffness, has been considered as an independent predictor of cardiovascular mortality in general population [1] and in subjects with end-stage renal disease [2], elderly people above 70 years [3], coronary heart disease, stroke [4] and essential hypertension [5]. Cf-PWV is also used for arterial stiffness risk stratification [6-8]. Arterial stiffening is a natural process, however premature stiffening occurs as a result of complex interactions between the pressure on endothelium from raised blood pressure, microvascular inflammation, oxidative stress and to a certain degree by the role of trace elements. Arterial stiffness can be both active and passive. The Extracellular Matrix (ECM) components in the arterial wall such as elastin and collagen determine the stiffness of the large elastic arteries. With age and disease, elastic fibres are degraded and fragmented, leading to increased stiffness of the arterial wall [9]. More than 30 elements (Cu, Zn, Mg, Mn, Cr, V and so on) were connected with the process of arteriosclerosis [10]. Trace elements such as magnesium, cobalt, lithium, vanadium, silicon, manganese, and thallium have been considered potentially beneficial, whereas cadmium, lead, silver, and antimony as potentially detrimental. Cobalt and zinc have been attributed both roles [11]. Essential trace element status was independently related to immune status, inflammation, and oxidative damage [12]. Factors such as diet, absorption ability, toxicities and drug-nutrient interactions play a vital role in maintaining a balance of the elements in the body [13]. With this background, the present cross-sectional study was conducted to assess the severity of arterial stiffness in apparently healthy population, and to evaluate the role of various risk factors and trace elements in the severity of arterial stiffness.

MATERIALS AND METHODS

This cross-sectional study was a part of the health camps conducted within the city (urban) and surrounding 27 villages (rural) of Nellore district during the years 2013-2016. This study comprises of both male and female subjects between 20-60 years, apparently normal as judged by the clinician basing on clinical and laboratory reference values, were included. Subjects were excluded if they had abnormal clinical, biochemical, serological, electrocardiographic particularly with conduction disorders and with the peripheral vascular disease, as these conditions interfere with the recording of pulse wave velocity. Additionally, pregnant and lactating women were also excluded. A total of 2800 subjects were screened among them 737 patients who were considered apparently healthy entered the study.

Institutional ethics committee approved the study protocol. Written informed consent was obtained from participants. All subjects underwent detailed physical and clinical examination. Height was measured using stature meter. Weight with calibrated weighing machine. Body Mass Index (BMI) was calculated using formula weight (kg)/height (m^2). ECG tracings were recorded. Blood pressure and pulse rate were recorded in the sitting position in the right arm with an electronic OMRON BP apparatus and the mean of the three readings was used as the final blood pressure recording. The cf-PWV (a marker of arterial stiffness) was measured using a volume plethysmographic arteriograph. (Periscope, M/S Genesis

medical systems, Hyderabad, Telangana, India). Typical values of PWV in the aorta range from approximately 5 to >15 m/s [14]. Based on the carotid femoral pulse wave velocity, arterial disease risk has been categorized into normal, mild, moderate and severe. Earlier studies have shown that there will be an increase in the PWV by 500cm/s when the arterial disease risk increases from Normal to Severe [15,16]. In the 2007 ESH/ESC hypertension guidelines published a fixed threshold value (12m/s) [17]. The 10ml of blood samples were drawn in vacutainers, transported to the laboratory, centrifuged and serum was stored in aliquots at -70 degrees until analysis of trace elements. Serum levels of Cu, Zn, Se, Cr, Al, Si, Mn, Mb, Vn and Pb were analysed using atomic absorption spectrometer (Shimadzu) with graphite furnace using manufacturer's recommendation.

STATISTICAL ANALYSIS

Data collected in predesigned case record forms were entered into Microsoft Excel 2007. Data was cleaned, stored and analysed using Microsoft pivotal tables. Descriptive data was mean, standard deviation, actual numbers, and percentages. Chi-square test and ANOVA with Bonferroni post-hoc test were used appropriately to test differences between proportions means between groups. A two tailed p-value less than 0.05 was considered statistically significant.

RESULTS

A total of 737 apparently healthy subjects participated in our study, 542/737 (73.5%) were from rural and the remaining participants 195/737 (26.5%) were living in urban areas, 328/737 (44.5%) were males, and 409/737 (55.5%) were females. Only 235/737 (31.9%) were in the age group of 51-60 years.

The severity of arterial stiffness was graded based on values of cf-PWV into four groups [15,16], among them 468/737 (63.5%) were having normal arterial stiffness, 107/737 (14.5%) mild, 57/737 (7%) moderate and 105/737 (14.2%) were having severe stiffness.

It can be seen from [Table/Fig-1] that the arterial stiffness severity was statistically similar between residential areas and gender. However, it was observed that a significant increase in PWV with increasing age.

Smoking, alcohol, blood pressures, and total cholesterol showed a linear trend across grades of arterial stiffness. However, a significant ($p<0.05$) trend was observed with cholesterol only. Triglycerides were not significant across grades of arterial stiffness. It was also found that, a significant and linear increase in systolic blood pressures across varying grades of arterial stiffness.

Among the trace elements, Cu, Al, and Vn were significantly different ($p<0.05$) across the severities of arterial stiffness, when

	All participants	Normal < 10 (m/s)	Mild 10-10.5 (m/s)	Moderate 10.5-12.0 (m/s)	Severe >12.0 (m/s)	p-value
Cf PWV (m/s)	10.92±0.13	9.89±0.16	10.15±0.13	11.89±0.12	12.04±0.14	0.001
Number	737(100%)	468 (63.5%)	107(14.5%)	57(7.73%)	105(14.2%)	0.001
Residential area						
Rural	542(73.5%)	332 (70.9%)	87 (81.3%)	43(75.4%)	80(76.2%)	0.14
Urban	195(26.5%)	136 (29.1%)	20(18.7%)	14(24.6%)	25(23.8%)	
Age						
20-30 yrs.	192(26.1%)	147 (31.4%)	31(29.0%)	10(17.5%)	4(3.8%)	0.001
31-40 yrs.	151(20.5%)	109(23.3%)	19(17.8%)	6(10.5%)	17(16.2%)	
41-50 yrs.	159(21.6%)	89(19.0%)	29(27.1%)	14(24.6%)	27(25.7%)	
51-60 yrs.	235 (31.9%)	123(26.3%)	28(26.2%)	27(47.4%)	57(54.3%)	
Gender						
Male	328(44.5%)	197(42.1%)	56(52.3%)	32(56.1%)	43(41.0%)	0.06
Female	409(55.5%)	271(57.9%)	51(47.7%)	25(43.9%)	62(59.0%)	
Trace elements						
Smokers	233(31.8%)	127(60%)	36(16.3%)	26(11.6%)	44(19.7%)	0.04
Alcoholics	228(31.5%)	97(42.1%)	56(52.3%)	32(56.1%)	43(19.7%)	0.03
Body Mass Index (Kg/m^2)	24.57±5.33	24.84±5.16	24.52±5.18	23.92±4.57	23.76±6.45	0.21
SBP mm Hg	137.19±45.23	115.88±6.57	118.72±7.85	124.80±4.04	132.28±5.24	0.001
DBP mm Hg	77.78±7.17	77.34±5.78	78.55±8.36	82.61±9.58	85.62±7.81	0.001
Fasting Sugar (mg/dl)	104.28±53.24	101.53±52.63	100.60±32.84	113.72±70.85	115.88±60.57	0.13
Total Cholesterol (mg/dl)	179.70±44.01	174.80±42.04	177.33±39.60	199.19±45.23	194.65±50.90	0.001
Triglycerides (mg/dl)	167.04±99.53	162.41±92.39	169.06±112.28	181.58±98.81	178.87±117.44	0.48
Trace elements						
Copper (Cu)	122.76±15.88	123.90±12.40	118.58±20.37	122.94±18.50	121.55±21.83	0.04
Zinc (Zn)	77.78±13.17	77.34±10.78	78.55±18.36	78.61±9.58	78.62±17.81	0.73
Selenium (Se)	55.79±8.21	55.80±7.97	56.59±8.14	56.14±8.22	54.87±9.36	0.61
Chromium (Cr)	26.41±9.02	26.09±8.91	27.92±9.41	26.91±9.66	26.29±8.92	0.46
Aluminium (Al)	1.92±0.31	1.89±0.26	1.95±0.30	1.89±0.29	2.04±0.48	0.001
Silicon (Si)	329.27±66.35	329.37±64.15	330.45±69.34	338.60±58.74	322.98±77.27	0.66
Manganese (Mn)	2.63±1.64	2.68±1.68	2.45±1.55	2.69±1.67	2.49±1.52	0.59
Molybdenum (Mb)	5.42±0.96	5.38±0.90	5.59±1.13	5.52±0.76	5.42±1.14	0.32
Vanadium (Vn)	14.97±12.97	15.48±13.03	13.76±12.84	15.38±14.17	13.48±12.22	0.04
Lead (Pb)	11.29±1.57	11.39±1.42	11.17±1.74	10.83±2.34	11.19±1.60	0.11

[Table/Fig-1]: Clinical and Trace nutrient levels across different grades of arterial stiffness.
Copper-(60-150µg/dL), Zinc-(80-120µg/L), Selenium- (55-65µg/L), Chromium- (33-40µg/L), Aluminium-(1.9-2.8µg/L), Silicon -(110-390µg/L), Manganese-(1.4-1.8µg/L), Molybdenum-(6-8µg/L), Vanadium-(4-8µg/L), Lead- (<20µg/L). BMI- BodyMass Index.

analysed using ANOVA. However, Chi Square test did not show any trend.

DISCUSSION

Arterial stiffening was recognised as an abstract marker for increased cardiovascular disease risk, including myocardial infarction, heart failure, and total mortality, as well as stroke, dementia, and renal disease [18,19]. The cf-PWV a quantitative measure of large artery stiffness, has been validated as a predictor of cardiovascular events in patients with hypertension as well as end-stage renal failure, diabetes, and most recently in middle-aged and older adults [8].

This study observed 36.5% of our participants had high arterial stiffness despite being apparently healthy. Age and blood pressure are the major determinants of PWV [20]. In our study too, it was observed that, severity in arterial stiffness is increasing with age and blood pressure, which were the fundamentals for increased arterial stiffness.

Reports have shown that it is marked even in the absence of an individual component of metabolic syndrome [21]. In our study, BMI and fasting blood sugars were similar across the severities of arterial stiffness. We found only two components of metabolic syndrome that use systolic blood pressures and total cholesterol showed a linear increase across grades of arterial stiffness.

In this study, more number of females had severe arterial stiffness. The literature says that gender differences in levels of metals exist and such differences may be associated with coronary risk [22]. It is also possible that females in our study group were elderly.

This study, detected that smokers, alcoholics were significant in numbers across grades of arterial stiffness. However, such a link was non-linear. Alcohol consumption induces oxidative stress and leads to lipid peroxidation. High alcohol intake predicts low antioxidant enzyme and that trace element may contribute to the increased susceptibility for the development of Coronary Artery Disease (CAD) [23]. Smoking accelerates the age-related decline in BP amplification and increases central arterial stiffness [24]. It is also possible that tobacco use and alcohol may cause autonomic dysfunction and increased pulsatile haemodynamic parameters. The alterations in pulsatile haemodynamics are the leading causes of elevated arterial stiffness and ventricular hypertrophy [25].

Copper levels were marginally declined across groups in our participants, and however, such a decline was non-linear, on another hand total cholesterol showed a linear trend across grades of arterial stiffness. Copper deficiency, as well as abundance, may increase the cholesterol content of the blood serum. It is possible thatin Cu-deficiency, the formation of the crosslinks of the elastin of the blood vessels is disturbed. Zinc deficiency may further aggravate the risk of arterial disease [21]. In our subjects, we observed a linear trend of increase in zinc levels which was not statistically significant. Zinc increases intracellular accumulation of Ca^{2+} ions, resulting in stiffened arteries, but its deficiency could reduce vasodilatation by signal transmission disturbances at the receptor level [26]. Zn is also considered a Ca^{2+} channel blocker [11].

Selenium, acting through the selenoprotein glutathione peroxidases, has critical roles in regulating antioxidant status. Reduced glutathione peroxidases could be related to increased generation of toxic lipid peroxides contributing to the endothelial dysfunction and arterial stiffness [27]. Selenium supplementation slows down the elastin degradation and degenerative changes of the vessel walls [28].

In our study, we noticed that fasting blood sugars and total cholesterol showed a linear trend across grades of arterial stiffness. However, such differences were not found in chromium and selenium levels across the severity of arterial stiffness. Chromium deficit may influence the arteriosclerotic process via the glucose tolerance factor [10]. High sugars reduced endothelial nitric oxide synthase (eNOS), Protein Kinase (PKG-1beta) and PKG activity. Cr (3+) prevented the effects of sucrose on Nitric Oxide (NO) signalling and promoting the BP-lowering effect [29]. Vanadium can overcome sucrose-induced elevation of SBP as well as some of the "genetic hypertension." different from chromium, this decrease was not overcome by high levels of dietary sucrose [30].

Aluminium is also considered as a mediator of oxidative stress; it increases the extra mitochondrial release of free oxygen radicals resulting in iron-induced lipid peroxidation and protein denaturation of cellular membranes in various organs [31]. Aluminium interferes with iron (Fe) absorption, use, or both and Aluminium levels are positively correlated with age in humans. Our study population showed variations in aluminium levels across different grades of arterial stiffness. However, such a trend was not linear. It is possible that drinking water by natural as well as water treatment processes could be a possible source of chronic Aluminium accumulation.

Silicon is found to be associated with vascular health and protection against atherosclerotic plaque formation. Soluble silica significantly reduced systolic blood pressure in spontaneously hypertensive rats, by stimulating the intracellular magnesium uptake [32]. Studies suggest that dietary silicon has no effect on atherosclerosis development and vascular health in the apo-E mouse model of diet-induced atherosclerosis, contrary to the reported findings in the cholesterol-fed rabbit model [33]. Another study indicated that Silicon-enriched spirulina improves early atherosclerosis markers in hamsters on a high-fat diet and synergy between spirulina and silicon [34]. Silicon effectively prevents gastrointestinal aluminium absorption [35].

Molybdenum, a co-factor, is essential for the function of sulphite oxidase, xanthine dehydrogenase, and aldehyde oxidase enzymes [36]. Xanthine dehydrogenase is nearly identical in structure and function to Xanthine oxidase (XO) catalyses the metabolic reactions leading from hypoxanthine to xanthine and from xanthine to uric acid. Serum Uric Acid (UA) represents a marker of inflammation and endothelial dysfunction. High uric acid levels indicate high serum molybdenum activity [37]. Uric acid is both pro and antioxidant, under circumstances, uric acid becomes pro-oxidant and induces an imbalance between endothelial NO and Reactive Oxygen Species (ROS) production, major contributes to endothelial dysfunction which plays an important part in arteriosclerosis [38]. Our study participants had molybdenum levels within reference ranges, and no significant difference was observed in the severity of stiffened arteries.

Manganese is a metal that functions as a co-factor for superoxide dismutase. Manganese regulates many enzymes and is essential for normal cell function. The manganese Superoxide dismutase (MnSOD), is an intra-mitochondrial enzyme that disposes of the superoxide anions generated by respiratory chain activity. It uses the potentially damaging free radicals of oxygen to make hydrogen peroxide, which quickly breaks down into water. Production of hydrogen peroxide occurs at a constant rate due to Mn-SOD activity [39]. It is possible that manganese too exerts its vasculoprotective activities via reducing oxidative stress. In our study population, there was no significant difference between various groups of arterial stiffness. One interesting finding is that all our study participants had manganese marginally high levels above the reference range, such levels can occur in a variety of environmental settings, nutritional sources, contaminated foods, infant formulas, and water, soil, and air with natural or man-made contaminations.

Lead directly interrupts the activity of enzymes, competitively inhibits absorption of essential trace minerals and deactivates antioxidant sulphydryl pools. Exposure to lead causes increase in local arterial stiffness [40]. None of our study participants had exposure above permissible limits.

LIMITATION

Analysis of trace elements in blood reflects absorption from all sources, including occupational exposure, diet, hobbies, medication, smoking, drinking water and local soil-containing dust. As this was a cross-sectional study, part of the data about the above information would have been missed while collecting the above data. Information regarding intake of antioxidants such as vitamin E, beta-carotene, and vitamin-C could not be obtained.

CONCLUSION

This study finds that 36.5% had high arterial stiffness despite being apparently healthy. Smoking, alcohol, blood pressures, fasting blood sugars, and total cholesterol, copper, aluminium, and vanadium could have contributed for such an abnormality. Caution has to be executed while interpreting our study results since the pathophysiological process is complex.

CONFLICT OF INTEREST

Dr. G. Subrahmanyam has received funding from Dr. Nandamuri Taraka Rama Rao University of Health Sciences, Vijayawada, Andhra Pradesh, for this study. Other authors declared that they had no conflict of interest.

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