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RESEARCH ARTICLE

Role of Vitamin D in pre-hypertension and its association with cellular senescence

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ABSTRACT

Background: Reports suggest that, in Indian subcontinent, there is 70–100% deficiency of Vitamin D (Vit-D), playing pivotal role in higher risk of development of bone diseases and several noncommunicable disease conditions such as malignancies, metabolic diseases, and cardiovascular disease. Reports on role of Vit-D on cellular senescence in pre-hypertension (pre-HTN) were not available. **Aims and Objectives:** The aims of the study were to explore the relationship between Vit-D and cellular senescence measured using the enzyme telomerase in pre-HTN. **Materials and Methods:** This investigation was carried out in 41 pre-hypertensives and equal number of age- and gender-matched controls. Cellular senescence was measured by increased levels of telomerase and Vit-D was assessed with using commercially available ELISA assay kits. **Results:** Weight and BMI, Systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP), mean arterial pressure (MAP), rate pressure product (RPP) and telomerase levels were high and vi-D levels were low in pre-HTN group. Low levels of Vit-D were negatively correlated with telomerase, HR, SBP, and PP. **Conclusion:** We concluded that the lower Vit-D levels in pre-HTN could lead to derangements in cardiovascular homeostatic mechanism and enhance the speed of cellular senescence measured by telomerase.

KEY WORDS: Cellular Senescence; Pre-hypertension; Telomerase; Vitamin D

INTRODUCTION

Deficiency of Vitamin D (Vit-D) is undertreated and pandemic yet under-diagnosed worldwide.[1-3] Reports suggest that, in Indian subcontinent, there is 70–100% deficiency of Vit-D, playing pivotal role in a higher risk of development of bone diseases and several noncommunicable diseases like cancer, metabolic diseases, and cardiovascular pathologies,[4] playing role as a major cause for higher health-care burden on Indian health-care system.[5-8]

Nowadays, this scenario leading to increased interest from research and clinical trials to examine the role in chronic diseased conditions. The CYP27B1 enzyme activation, receptor of Vit-D was recognized in several cells which are not the components of calcium and phosphorous homeostasis.[9] This increased the focus on the role of D vitamin in various physiological actions. Information is not available to demonstrate the role of D vitamin in cellular processes.[10,11]

In May 2003, the joint national commission (JNC 7), to emphasize the perception of close abnormal blood-pressure levels, introduced the term pre-hypertension (pre-HTN) which described as 120–139 mmHg of systolic blood pressure (SBP)

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of 80–89 mmHg of diastolic blood pressure (DBP).[12,13] It helps such pre-HTN individuals could modify their lifestyle to postpone hypertension.[14] Reports have demonstrated that pre-HTN caused higher risk if cardiovascular morbidity independent to other risk factors.[13,15]

Many original research articles, reviews, and meta-analyses reported the pre-HTN prevalence in varied groups and its relation with risks and benefits of treatment in cardiovascular diseases. The prevalence of pre-HTN in India ranges from 20 to 80%.[16,17] In reports belongs to nine states of south Indian adults above 20 years of age, 42.4% of male and 39% females had pre-HTN.[18] Another report from Lucknow with 1746 population in this study, they reported 32.3% pre-HTN,[16] A Puducherry based study with 300 medical college staff had reported prevalence of 22%[17] another report from Uttar Pradesh showed 27.2% prevalence.[19] In military adults, the the highest prevalence of 80% was reported.[20] With 500 medical students in Karnataka reported a higher prevalence of 55%.[21]

The telomerase is an enzyme to inhibit the telomere shortening process. Telomeres become short with each cell division and this process reaches a crucial extent leads to replicative cellular senescence.[22,23]

Information on the importance of Vit-D in cellular senescence in individuals with pre-HTN was not available. Hence, in this study, we planned to explore the link between Vit-D and cellular senescence measured with the enzyme telomerase in pre-HTN. Further, an attempt was made to describe the importance of Vit-D in blood pressure.

MATERIALS AND METHODS

After obtaining the institute ethics committee clearance from Sri Venkateswara Medical College, Tirupati, volunteers were recruited from medical and paramedical students.

Inclusion criteria for the pre-hypertensive group (pre-HTN) (n = 41) were both genders between 18 and 25 years of age with SBP between 120 and 139 mmHg and DBP between 80 and 89 mmHg in apparently healthy individuals.

The controls (n = 41) population were healthy individuals with 18–25 years of age with SBP between 100 and 119 mmHg and DBP between 60 and 79 mmHg.

Individuals suffering from diabetes, hypertension, endocrine disorders, kidney diseases, and hypertensive patients already receiving medication were not considered to take part in this research.

Sample Collection

The volunteers were asked to not participate in heavy exercises, not drink alcohol and coffee 1 day before the data collection. Baseline, anthropometric parameters were recorded before recording of the BP by sphygmomanometer as per standard protocol.[24]

Then, 5 ml of blood was collected, allowed to clot, and subjected to centrifugation to separate the serum. Serum was stored at –80°C for processing of Vit-D and telomerase levels as per the instructions provided in the commercially available kits.

Statistical Analysis

R 3.2.3 for Windows was used to analyze the data. To study the between-group differences, independent *t*-test, to assess the correlation of Vit-D with telomerase and other parameters, Pearson's correlation coefficient analysis was applied.

RESULTS

The study population included 82 apparently healthy individuals. Forty-one of 82 were pre-hypertensives with the age of 18.61 ± 0.70 and the age of controls was 18.80 ± 0.95. Among 41 in each group, 26 males, 15 females in pre-HTN group and 21 males, 20 females in the control group. Table 1, a significant difference, was not found between-group differences in height and waist-hip ratio. However, pre-HTN group subject's BMI ($P < 0.000$) and weight ($P < 0.000$) was more compared to controls. Mean and standard deviation of various cardiovascular parameters are given in Table 2. In pre-HTN group, significantly higher HR ($P < 0.000$), SBP ($P < 0.000$), DBP ($P < 0.000$), MAP ($P < 0.000$), and RPP ($P < 0.000$) were seen when compared to controls. No

Table 1: Comparison of anthropometric characteristics between pre-HTN and controls

Parameter	Pre-HTN (n=41)	Controls (n=41)	*P*-value
Age	18.61±0.70	18.80±0.95	0.481
Gender (male/female)	26/15	21/20	NA
Height (cm)	164.25±8.58	162.70±7.95	0.403
Weight (kg)	67.53±11.89	55.63±9.65	0.000
BMI (k/m^2)	24.96±3.62	21.14±4.19	0.000
Waist to hip ratio	0.83±0.05	0.82±0.11	0.522

Table 2: Comparison of cardiovascular parameters between pre-HTN and controls

Parameter	Pre-HTN (n=41)	Controls (n=41)	*P*-value
HR (BPM)	87.90±3.95	79.65±3.03	0.000
SBP (mmHg)	124.09±4.29	113.5±4.55	0.000
DBP (mmHg)	84.44±3.70	75.41±3.47	0.000
PP (mmHg)	39.65±6.33	38.09±4.14	0.191
MAP (mmHg)	97.65±2.51	88.11±3.33	0.000
RPP	10914.83±715.55	9041.80±495.93	0.000

significant difference was seen in PP but it was slightly high in pre-HTN group and negatively associated with Vit-D (r: –0.379).

Table 3 depicts the values of Vit-D, telomerase in both groups. Significantly low levels of Vit-D ($P < 0.000$) and high telomerase ($P < 0.000$) were seen in pre-HTN group when compared to controls. Table 4 shows the correlation of Vit-D and other parameters in pre-HTN group. Low levels of Vit-D have no correlation with BMI, waist-hip ratio, DBP, and MAP. However, significant correlation was seen with HR (r: –0.301), SBP (r: –0.566), PP (r: –0.379), RPP (r: 0.499), and telomerase (r: –0.383).

Further, as shown in Table 5, high telomerase levels have correlation with waist-hip ratio (r: 0.342), SBP (r: 0.495), DBP (r: 0.450), MAP (r: 0.669), and RPP (r: 0.322) but no significant correlation was seen with BMI, HR, and PP.

Table 3: Comparison of Vitamin D and telomerase levels between pre-HTN and controls

Parameter	Pre-HTN (*n*=41)	Controls (*n*=41)	*P*-value
Vitamin D (ng/ml)	17.60±4.70	20.38±7.96	0.058
Telomerase (IU/ml)	37.07±18.54	7.80±3.30	0.000

Table 4: Correlation between Vitamin D and other parameters in pre-HTN

Parameter	Vitamin D (ng/ml)	
	r-value	*P*-value
BMI (kg/m^2)	0.105	0.501
Waist hip ratio	0.216	0.165
HR (BPM)	–0.301	0.050
SBP (mmHg)	–0.566	0.000
DBP (mmHg)	0.230	0.137
PP (mmHg)	–0. 379	0.012
MAP (mmHg)	–0.100	0.523
RPP	0.499	0.001
Telomerase (IU/ml)	–0.383	0.011

Table 5: Correlation between telomerase and other parameters in pre-HTN

Parameter	Telomerase	
	r-value	*P*-value
BMI (kg/m^2)	0.226	0.144
Waist-hip ratio	0.342	0.025
HR (BPM)	0.134	0.392
SBP (mmHg)	0.495	0.001
DBP (mmHg)	0.450	0.002
PP (mmHg)	0.054	0.730
MAP (mmHg)	0.669	0.000
RPP	0.322	0.035
Vitamin D (ng/ml)	–0.383	0.011

DISCUSSION

This study volunteers had no statistically significant variations in their age, height, and waist-hip ratio. Weight and body mass index were significantly high in the pre-HTN group when compare to age- and gender-matched controls. HR, SBP, DBP, PP, MAP, RPP, and telomerase levels were high, Vit-D levels were low in the pre-HTN group. Low Vit-D levels were negatively correlated with telomerase, HR, SBP, and PP and it was independent of age, gender, BMI, and waist-hip ratio.

Earlier reports have shown that higher Vit-D is related to longer telomere length, which underscores the conceivably advantageous impacts of this hormone on cell senescence and age-related conditions.[25] In this study, cellular senescence was assessed using telomerase. This enzyme attempts to inhibit the process of telomere shortening.[22,23] Since the cell telomere loss appears to result from cell division just to a fractional degree, different components, particularly oxidative stress, were attested to assume a job in the expanded rate for shortening of telomeres.[26,27] The exact mechanism by which lower Vit-D levels are associated with this cellular senesce is hypothesized dependent on the perceptions recommends that the degrees of the telomerase may really be related to oxidative stress, with higher oxidative stress prompting higher telomerase levels. Cells of nearly complex organism may not have an ability to divide. This marvel was depicted by Hayflick in 1961.[28] The quantity of potential divisions – around fifty – was named the "Hayflick Limit" and at times is called cell senescence. Just because it was valued that cells could be mortal (typical cells) or unfading (tumor cells). The results of our study showed an association between Vit-D and BP is consistent with previously conducted studies[29,30] and stretch out the relationship to pre-HTN, a prior stage when essential anticipation is powerful. Zhao *et al*.[31] in an ongoing report detailed a positive relationship between Vit-D and hypertension and pre-HTN. Forman *et al*.[29] reported a positive relationship between Vit-D and self-revealed occurrence hypertension among 38,388 men from the Health Professionals' follow-up study and 77,531 females from the Nurses' Health Study; a positive affiliation was likewise detailed between Vit-D and hypertension in a subsample of members. Further, a study concentrate from the second Nurses' health study detailed a positive relationship between serum Vit-D and hypertension among 1484 young females.[29] In the NHANES, SBP was demonstrated to be conversely connected with Vit-D among 12,644 participants.[30] Notwithstanding, not all investigations have indicated a reliable positive relationship between low Vit-D and BP. In a planned report directed in the UK, Forouhi *et al*.[32] did not locate a huge relationship between serum Vit-D

and BP in a moderately aged associate of 524 non-diabetic people. In another examination led by Jorde *et al*.,[33] serum Vit-D levels were emphatically connected with SBP yet had no prescient incentive for the improvement of hypertension or changes in BP. Hardly any intercession preliminaries have announced that Vit-D supplementation did not diminish BP in explicit populaces, including postmenopausal[34] and overweight individuals.[35] Several mechanisms have been proposed to explain the relationship between lower Vit-D levels and pre-HTN. Earlier reports have demonstrated the expanded enactment of the renin-angiotensin-aldosterone framework in Vit-D receptor.[36] Low Vit-D likewise advances insulin resistance,[37] endothelial dysfunction,[38] production of pro-inflammatory cytokines,[39] hyperparathyroidism, and hypocalcemia influencing vascular smooth muscles.[40]

Strength and Limitations

The uniqueness of this study is that, we have explored the association of Vit-D with cellular senesce in pre-HTN individuals. This will be helpful to identify and develop strategies to overcome the early development of cardiovascular disease, cellular ageing, and other noncommunicable diseases. However, due to the cross-sectional nature of our study limits causal inferences. Further, we are planning to extend the study to explore the role of oxidative stress, parathyroid hormones which could confound the observed association.

CONCLUSION

Based on our results, we conclude that reduced Vit-D levels in pre-HTN may cause derangements of cardiovascular homeostatic mechanism, enhance the speed of cellular senescence measured by telomerase. Nevertheless, since this is a preliminary investigation, larger investigations with varied aged groups, across geographical distribution, professional, and socioeconomic differences.

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