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Relationship of Serum Retinol and Vitamin B_{12} to Essential Hypertension - An Observational Study in Eastern India

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ABSTRACT

Pathophysiology of essential hypertension has been linked to various factors including nutrition. 139 essential hypertension cases were divided into group 1 (67 younger cases, <50 years of age) and group 2 (72 older cases, more than 50 years of age. Serum retinol and vitamin B12 levels of the 139 cases and 127 nonhypertensive controls were assayed. There was no significant difference between the mean levels of serum vitamin B_{12}levels of cases and controls, though the levels of serum vitamin B_{12}were decreased in cases in comparison to controls. But, mean levels of serum retinol were significantly decreased in cases with respect to controls, and the decrease was more significant in older patients when compared to younger patients. Levels of serum retinol are decreased in essential hypertension and this decrease is more as age advances, but levels of serum vitamin B_{12} are unchanged in essential hypertension. Retinol may be used as a marker for essential hypertension, though further studies in this regard are required to validate the present observations.

Keywords: Essential hypertension, serum retinol, vitamin B12

INTRODUCTION

Essential hypertension can be defined as a rise in blood pressure of unknown cause that increases risk for cerebral, cardiac, and renal events. Subtle target-organ damage such as left-ventricular hypertrophy, microalbuminuria, and cognitive dysfunction takes place early in the course of hypertensive cardiovascular disease, although catastrophic events such as stroke, heart attack, renal failure, and dementia usually happen after long periods of uncontrolled hypertension only. [(1)] Hypertension is directly responsible for 57% of all stroke deaths and 24% of all coronary heart disease deaths in India. At an underestimate, there are 31.5 million hypertensives in rural and 34 million in urban populations. [(2)]

The pathophysiology of essential hypertension depends on the kidney, central nervous system, endocrine factors, the large arteries, and the microcirculation, but mostly arises as a complex quantitative trait that is affected by varying combinations of genetic and environmental factors. [(3)] There is still much uncertainty about the pathophysiology of hypertension. A small number of patients (between 2% and 5%) have an underlying renal or adrenal disease as the cause for their raised blood pressure. In the remainder i.e. 95%-98%, however, no clear single identifiable cause is found and their condition is therefore labelled "essential hypertension". In the past few years, factors other than the traditional or commonly known factors have been evaluated, including endothelial dysfunction (as manifested by changes in endothelin and nitric oxide), low birth weight and

intrauterine nutrition, and neurovascular anomalies. [4] Studies on vitamin D intake and BP have suggested that dietary vitamin D may reduce BP or risk of hypertension. [5,6] Other studies have found that disturbed folate and homocysteine metabolism may play a role in the early stages of hypertension. [7] Thus, nutrition plays a role in the pathophysiology of hypertension.

These facts prompted the authors to conduct an investigation on the levels of serum retinol and vitamin B_{12}in adults with essential hypertension.

MATERIALS AND METHODS

The study was a hospital-based case–control study conducted in a tertiary care medical college and hospital in West Bengal, India. The study was approved by the Institutional Ethical Committee. Before enrollment of the subjects, informed consent was obtained from all the participants. The duration of the present study was 10 months and included 139 essential hypertension patients attending the outpatient department during the above mentioned period. These patients were further divided into group 1 (67 younger patients, <50 years of age) and group 2 (72older patients, more than 50 years of age). 127 age- and sex-matched patients attending outpatient department, characterized by the absence of hypertension or family history of hypertension, served as controls. Consecutive patients attending the OPD and satisfying inclusion criteria were selected assuming that the patients attended OPD randomly. Exclusion criteria included participants who had secondary hypertension from various causes, cholestasis, unusual dietary habits, acute or chronic infections, fever, malabsorption syndromes, oral supplements or drugs-containing vitamin A and vitamin B12 during the past 6 months and topical application of vitamin Aduring the preceding 1 month. Complete history and physical examination of all cases and controls were undertaken.

After overnight fasting venous blood samples were collected from all subjects, serum separated and transferred in ice blocks. The samples were then stored at −20°C until the biochemical assay. All samples were coded and assayed in a blind fashion by an investigator who was unaware of the participant's clinical status. Serum retinol and vitamin-B12 levels were assayed by RP-HPLC. Statistical analysis of data was performed using SPSS software version 20 (IBM, New York, USA), and inferences were drawn. A value of $p < 0.05$ was considered to be statistically significant and $p < 0.001$ highly significant.

RESULTS

Table 1. Serum levels (as Mean ± SD) of retinol (in mcg/dl) and vitamin B_{12} (in pg/ml)

	retinol	vitamin B_{12}
Cases: group 1	287±23	519±43
Cases: group 2	284±31	517±48
Controls	293±18	528±32

Number of subjects: Group 1 – 67, group 2 – 72, controls- 127

For vitamin B_{12} levels:

1. Student t test to test for significance between controls and group 1:
p value and statistical significance:
The two-tailed p value equals 0.1009
By conventional criteria, this difference is considered to be not statistically significant.
Confidence interval:
The mean of group 1 minus controls equals -9.00
95% confidence interval of this difference: From -19.77 to 1.77
Intermediate values used in calculations:
t = 1.6483
df = 192
standard error of difference = 5.460
SEM values are 5.25 and 2.84 for group 1 and controls

2. Student t test to test for significance between controls and group 2:
p value and statistical significance:
The two-tailed p value equals 0.0545

By conventional criteria, this difference is considered to be not quite statistically significant.
Confidence interval:
The mean of group 2 minus controls equals -11.00
95% confidence interval of this difference: From -22.21 to 0.21
Intermediate values used in calculations:
t = 1.9347
df = 197
standard error of difference = 5.685
SEM values are 5.66 and 2.84 for group 2 and controls

For retinol levels:

1. Student t test to test for significance between controls and group 1:
p value and statistical significance:
The two-tailed p value equals 0.0468
By conventional criteria, this difference is considered to be statistically significant.
Confidence interval:
The mean of group 1 minus controls equals -6.00
95% confidence interval of this difference: From -11.92 to -0.08
Intermediate values used in calculations:
t = 2.0007
df = 192
standard error of difference = 2.999
SEM values are 2.81 and 1.60 for group 1 and controls

2. Student t test to test for significance between controls and group 2:
p value and statistical significance:
The two-tailed p value equals 0.0102
By conventional criteria, this difference is considered to be statistically significant.
Confidence interval:
The mean of group 2 minus controls equals -9.00
95% confidence interval of this difference: From -15.84 to -2.16

Intermediate values used in calculations:
t = 2.5930
df = 197
standard error of difference = 3.471
SEM values are 3.65 and 1.60 for group 2 and controls

DISCUSSION

In the present study there was no significant difference between the mean levels of serum vitamin B_{12} levels of cases and controls, though the levels of serum vitamin B_{12}were decreased in cases in comparison to controls. But, mean levels of serum retinol were significantly decreased in cases with respect to controls, and the decrease was more significant in older patients (p = 0.0102 for group 2) when compared to younger patients (p = 0.0468 for group 1), as depicted in table 1.

Hypertension is a major contributor to the development of renal failure, cardiovascular disease, and stroke. These pathologies are associated with vascular functional and structural changes including endothelial dysfunction, altered contractility, and vascular remodeling. Central to these phenomena is oxidative stress. Factors that activate pro-oxidant enzymes, such as NADPH oxidase, remain poorly defined, but likely involve angiotensin II, mechanical stretch, and inflammatory cytokines. Reactive oxygen species influence vascular, renal, and cardiac function and structure by modulating cell growth, contraction/ dilatation, and inflammatory responses via redox-dependent signaling pathways. [8] Increased vascular reactive oxygen species production, especially superoxide anion, contributes significantly in the functional and structural alterations present in hypertension. An enhanced superoxide production causes a diminished NO bioavailability by an oxidative reaction that inactivates NO. Exaggerated superoxide levels and a low NO bioavailability lead to endothelial dysfunction and hypertrophy of vascular cells. It has been shown that the enzyme NAD(P)H oxidase plays a major role as the most important source of superoxide anion in vascular cells. [9] Potential sources of excessive ROS in

hypertension include nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, mitochondria, xanthine oxidase, endothelium-derived NO synthase, cyclooxygenase 1 and 2, cytochrome P450 epoxygenase, and transition metals. Antioxidants including Vitamins A, C and E, L-arginine, flavanoids, and mitochondria-targeted agents (Coenzyme Q10, acetyl-L-carnitine, and alpha-lipoic acid) have been used to decrease hypertension or its risk. [(10)] In whole blood and in mononuclear cells from hypertensive subjects, Redon et al found an increase in oxidative stress and a reduction in the activity of antioxidant mechanisms that appeared to be independent of the blood pressure values. [(11)] Engelhard et al found that treatment with antioxidant-rich tomato extract can reduce blood pressure in patients with grade-1 HT, naive to drug therapy. [(12)] Interest in vitamin A-related compounds focus primarily on beta-carotene, given promising epidemiological data with respect to its cardioprotective effects and a correlation of higher plasma levels to lower blood pressure in men. [(13)] Thus, the authors think that the decreased levels of retinol in the present study are probably a result of relative exhaustion of antioxidant capacity in hypertension due to excess free radicals, and this exhaustion is more pronounced as the process of hypertension progresses with age. This is apparent by the levels of retinol, which are decreased further in the older subset of patients (group 2) when compared to the younger patients (group 1).

Vitamin A (retinol) and its analogs (retinoids) are important regulators of cell proliferation, differentiation, immune function, and apoptosis. Retinoic acid (RA), a vitamin A metabolite, is involved in embryonic kidney patterning through the control of receptor tyrosine kinase expression, which modulates ureteric bud branching morphogenesis. Humans at the low end of nephron number are predisposed to primary hypertension. Because RA regulates nephron mass, its optimal availability during nephrogenesis is critical. RA levels in the embryo are affected by several factors, such as maternal vitamin A nutrition and disturbances in retinol metabolism. Maternal vitamin A deficiency during pregnancy is widespread in developing countries and segments of these populations may be exposed to low vitamin A during fetal life when nephron number is determined. Infants are likely to be born with suboptimal nephrons and may develop primary hypertension later in life. [(14)] Whether this data is relevant to the present work can be determined only by further research.

This study has limitations that must be considered. To assess retinol and vitamin B_{12}, RP-HPLC was used. Retinol and vitamin B_{12} can be estimated by various methods, but the present method was employed as it is the most commonly used, time tested and standard method. Also, number of patients in the study groups was not large. Thus, care must be taken in extrapolating the present findings to other populations. Patients were taking a number of medications to control hypertension. However, these treatments are characteristic of patients with hypertension and do not affect serum retinol and vitamin B_{12} levels. Despite these limitations, we believe that our study points towards using retinol as an important, promising antioxidant marker for hypertension. As our findings point to a decrease in the antioxidant retinol, the problem of oxidative stress in hypertension should also be further investigated in a larger number of patients, and other markers of oxidative stress and antioxidants should be assessed.

CONCLUSION

Levels of serum retinol are decreased in essential hypertension and this decrease is more as age advances, but levels of serum vitamin B_{12} are unchanged in essential hypertension. Retinol may be used as a marker for essential hypertension, though further studies in this regard are required to validate the present observations.

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