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Vitamin D Status, Insulin Resistance and Arterial Stiffness in Normal Healthy Subjects

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Abstract
Vitamin D deficiency is common worldwide. Presence of vitamin D receptors on various tissues, explains its diversity of actions. Reduced levels of vitamin D is associated with insulin resistance (IR), diabetes, arterial stiffness and Cardio vascular disease (CVD) risk. This study was done to find out the association between hypovitaminosis D, IR and arterial stiffness. 50 normal healthy individuals, between 18 – 60 yrs of age (males & females) were selected randomly, as study subjects . Blood pressure was recorded by sphygmomanometer. Fasting plasma and serum samples were collected for estimating Glucose, Total cholesterol, triglycerides , Insulin, 25 (OH) D, Insulin resistance calculated by HOMAIR .Arterial stiffness was measured by Sphygmo Cor analyser. Indices of arterial stiffness were Augmentation Index (AIx), Pulse wave velocity (PWV), Sub Endocardial Viability ratio (SEVR). The subjects were divided into 2 groups based on 25(OH) D levels. group 1 (</= 20 ng/ml) , group 2 (>20ng/ml). All the parameters were compared between the groups. Statistical analysis was done by Students t test, Pearson's correlation. 58% of the subjects were having Vitamin D deficiency. p value was significant for iPTH (0.03) and AIx (0.02). Inverse correlation was found between 25(OH) D and HOMIR (r = - 0.134). Our study concludes that vitamin D deficiency is common in normal healthy individuals. Hypovitaminosis D may lead to increased arterial stiffness & IR which will increase the future risk for CAD. Supplementation with Vitamin D may be beneficial for preventing CAD.

Keywords: *Vitamin D, HOMAIR, Augmentation Index, iPTH.*

Introduction

Vitamin D deficiency is highly prevalent all over the world. A study from Goswami et al showed that vitamin D deficiency is prevalent in Indians[1]. Vitamin D deficiency is associated with hypertension, insulin resistance, left ventricular hypertrophy, CVD and overall mortality in the general population[2]. vitamin D influences endothelial and smooth muscle cell function, mediates inflammation and modulates Renin-Angiotensin – Aldosterone axis[3]. Vitamin D status is assessed by measuring 25 (OH) D. Decreased vitamin D is associated with abnormalities in indices of arterial stiffness with larger Augmentation Index (AIX), pulse wave.

Materials & Methods

The study included 50 normal healthy individuals, the staff and employees of Narayana Medical College and Hospital. The subjects were 18- 60 yrs of both gender. The study protocol was approved by Institutional Ethical Committee. Informed written consent was taken from all the study subjects. Fasting serum and plasma samples were collected for analysis. Biochemical Parameters included were Fasting plasma glucose- GOD POD method, Total Cholesterol, Triglycerides - enzymatic end point method. Fating insulin – Chemiluminescence method. Insulin resistance – HOMA IR method, 25 (OH) D - Chemiluminescence method.

Arterial Stiffness

After an initial rest period of 10 min, average blood pressure of three readings was taken. Pulse wave velocity, Augmentation index and sub endocardial viability index ratio derived with Sphygmo Cor device. The set up consists of a hand held tonometer attached to a device and a laptop computer. High fidelity sequential pressure wave forms are obtained by placing the tonometer on the radial artery of the dominant wrist. The device then applies transfer function to these peripheral measurements to estimate central (aortic) pressure parameters and degree of augmentation secondary to reflected wave from periphery. This permits derivation of AIx (augmented pressure/ total central pulse pressure) and Sub Endocardial Vibility Ratio (SEVR) (area under diastolic phase / systolic phase). Pulse Wave Velocity, can be determined by acquiring wave forms at the carotid and femoral sites with electrocardiogram gating. Velocity in mt /sec, calculated by measuring the interval between ECG R wave and the recorded wave forms at each site, where as distance between sites measured manually[4].

Results

The study subjects were divided into 2 groups based on 25(OH) D status . Group 1 with 25(OH) D </= 20 ng/ml and Group 2 with 25(OH) D > 20ng/ml .All the study parameters were compared between the groups. Statistical analysis was done by graph pad prism software . Results were expressed as Mean ± SD and p value < 0.05 was considered significant. Correlation between IR and Viamin D expressed as Correlation co efficient Table 1: Shows the biochemical parameters & arterial stiffness indices with p value between the groups. Among all the parameters there is significant difference in iPTH (p = 0.03) and AIx(p= 0.02). Fig 1 shows a negative correlation between 25(OH) D and IR with r value of - 0.134.

Fig 1: Correlation graph between 25 (OH) D and Insulin resistance.

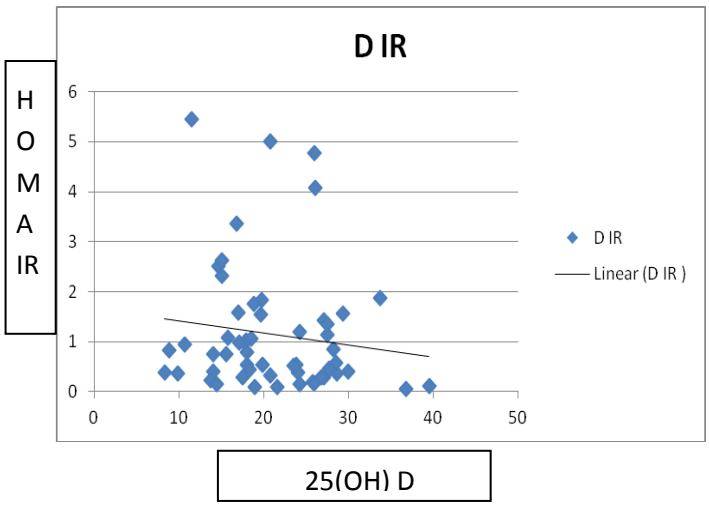

Table 1: Comparison of biochemical and arterial stiffness indices between group 1 & 2.

Parameters	Group 1 n = 29 Mean ± SD	Group 2 n= 21 Mean ± SD	p value
25(OH) D ng/ml	15.70 ± 3.28	27.15 ± 4.27	0.000
Fasting glucose mg/dl	80.82 ± 24.4	82.59 ± 23.6	0.78
Fasting Insulin mIU/L	5.53 ± 3.94	4.19 ± 4.45	0.24
HOMA IR	1.22±1.15	1.06± 1.37	0.63
PTH ng/L	39.34± 28.4	26.18±15.45	0.03
Calcium mg/dl	9.6±0.75	9.75±1.06	0.55
Phosphorus mg/dl	6.25±2.2	7.4±2.47	0.07
ALP IU/L	243.75±72.5	222.5± 59.3	0.24
Triglycerides mg/dl	140.93± 74.50	169 ± 67.5	0.14
Total cholesterol mg/dl	175.1± 40.9	171.85± 31.43	0.74
hs CRP mg/L	2.78 ± 1.92	3.78 ± 3.34	0.17
AIx augmentation index	0.24±0.1	0.19±0.05	0.02
Systolic BP mmHg	126.20±9.41	123.7±10	0.34
Diastolic BP mm Hg	82.06±6.19	82.03±6.68	0.98
SEVR	1.50±0.13	1.4±0.09	0.07

Discussion

Vitamin D deficiency is not uncommon in India [5]. Vitamin D deficiency is an emerging risk factor for various cardiovascular diseases, vitamin D inadequacy contributes a largely unrecognized epidemic in many populations worldwide [6]. Vitamin D causes changes in the vascular smooth muscle and also regulates RAAS, causing supper-ssion of renin gene [7]. Vitamin D down regulates the production of inflammatory cytokines [8]. In response to inflammatory signals, C- Jun N terminal kinase (JNK) are activated and can target IRS -1 for serine phosphorylation and inhibits the insulin receptor signaling cascade , leading to Insulin Resistance [9].

Low vitamin D levels in US adolescents were strongly associated with important risk factors for CAD like increased BP, fasting hyperglycemia, and metabolic syndrome[10]. Deficiency of vitamin D is associated with worse vascular endothelial function. Vascular endothelial dysfunction and arterial stiffness precede and contribute to the development of CVD [11]. According to a study by M. Zagura et al, arterial stiffness and abnormal vitamin D levels contribute to vascular calcification in patients with Peripheral artery Disease and in healthy individuals [12,13]. Consistent with the above findings our study proved that normal healthy individuals with 25(OH) D deficiency had higher Augmentation Index and SEVR. Hence those with vitamin D deficiency are prone for CAD. Surrogate measures of arterial stiffness indicate that arterial stiffness increases both with age and in certain disease states like diabetes mellitus, end stage renal failure[14]. Decreased vitamin D and increased PTH are commonly encountered in CKD and it is also recognized that these abnormalities are more wide spread in general population. By our study, we also observed significant difference in iPTH levels between the two groups and those with deficiency of Vitamin D had increased AIx and raised PTH. As the sample size is small we could not prove the association between iPTH and AIx. Arterial calcification is an independent predictor of vascular morbidity and mortality in general population and also is a marker of sub clinical atherosclerotic disease[15,16]. As the various techniques are less expensive and more widely available, the measurement of arterial stiffness could become routine in primary care settings and in hospital practice. Decreased 25(OH) D and increased arterial stiffness has been proposed as a common pathway by which insulin resistance syndrome leads to increased CVD risk .Lack of calcitriol results in an increase in PTH levels. Excess PTH may at least in part promote CVD by increased cardiac contractility, chronic atherosclerosis via insulin resistance [17]. Several cross sectional studies have shown the existing

inverse relationship between serum Vitamin D and glycemic status measures. Our study also showed negative correlation between vitamin D and insulin resistance by HOMA IR method. Altered insulin signaling in endothelial cells has emerged as an important mechanism for the increased susceptibility to CVD[18]. Various supporting studies suggests that vitamin D deficiency is associated with Insulin Resistance or impaired insulin secretion[19]. A study by Alemzadeth et al showed that vitamin D levels were positively associated with insulin sensitivity, suggesting possible role for pathogenesis of CAD and diabetes. There is evidence that vitamin D may influence insulin sensitivity through insulin receptor expression regulation of intracellular calcium [20,21]. Hence forth there is a link between vitamin D deficiency, Arterial stiffness and insulin resistance, which have to be given proper care even in normal healthy individuals to prevent Cardiovascular diseases.

Conclusion

By our study we conclude that there is negative correlation between 25 (OH) D and Insulin resistance (HOMA IR). Subjects with vitamin D deficiency had higher AIx and SEVR suggesting that vitamin D deficiency / insufficiency may lead to CAD. The study will be useful to assess the cardiovascular risk apart from traditional risk factors for CAD. As vitamin D prophylaxis and treatment stratagies are easy to implement, the deficiency status can be corrected to reverse the stiffening of vessels and prevent insulin resistance.

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