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Vitamin D And Chronic Periodontitis – A Randomised Double Blinded Placebo Controlled Parallel Clinical Trial.

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Abstract:
Background: *Vitamin D is crucial for a wide variety of organ systems; nevertheless, evidence has demonstrated that vitamin D deficiency may place subjects at risk for not only low mineral bone density /osteoporosis and osteopenia but also infectious and chronic inflammatory diseases Vitamin D also has anti-inflammatory effects by suppressing pro-inflammatory cytokines through its effect on bone and mineral metabolism, innate immunity and several VDR gene polymorphisms, vitamin D has been reported to be associated with periodontal disease.*
Objectives: *To assess anti-inflammatory effect of vitamin D3, when administered as monotherapy in generalised chronic periodontitis.*
Methods: *This study comprises of 56 patients of generalised chronic periodontitis who were screened for their serum vitamin D3 levels. Out of which 30 patients who were vitamin D3 deficient (<20ng/ml) formed the study group. They were randomly given either vitamin D3 supplement or placebo. The Periodontal parameters and RVG were taken before treatment and post treatment after 2 months.*
Results: *The results of this study indicate a probing pocket depth reduction in the vitamin D supplement group. The post-treatment pocket depth is 5.3472 compared to 5.7661 in the pre-treatment group. A correlation of 0.667 and statistically significant ($p<0.002$) reduction in pocket depth is noted. Clinical attachment gain in the post-treatment group was 35.61 compared to the pre-treatment mean value 33.72 indicating a statistically significant gain in the clinical attachment ($p<0.000$).*
Conclusion: *Vitamin D deficiency may place subjects at risk for not only low bone mineral density/osteoporosis and osteopenia, but also infectious and chronic inflammatory diseases like periodontitis.*
Keywords: *periodontitis, proinflammatory cytokines, vitamin D receptor.*

I. Introduction

Traditionally, vitamin D has been associated with bone health, and it is well understood that vitamin D deficiency leads to rickets in children and osteomalacia, osteoporosis in adults. However, it is now known that adequate vitamin D status is important for optimal functioning of many organs and tissues throughout the body, including the cardiovascular (CV) system. Vitamin D deficiency in addition to playing an important role in the genesis of coronary risk factors and Cardio vascular diseases also predisposes to hypertension, diabetes, the metabolic syndrome, left ventricular hypertrophy, congestive heart failure, and chronic vascular inflammation. Vitamin D also has anti-inflammatory effects by suppressing pro-inflammatory cytokines, IFN-γ, TNF-α, and IL-12. Through its effect on bone and mineral metabolism, innate immunity, and several vitamin D receptor gene polymorphisms, vitamin D has been reported to be associated with the periodontal diseases. The aim of this randomised double-blinded placebo controlled parallel clinical trial was, to evaluate the serum level of vitamin D3 among chronic periodontitis patients and to assess the outcome of vitamin D3 monotherapy on periodontal status in chronic periodontitis patients who were deficient in vitamin D3 levels.

II. Materials and Methods

This study comprises of 56 patients of generalised chronic periodontitis who were screened for their vitamin D3 levels by serum. Out of which 30 patients who were vitamin D3 deficient (<20ng/ml) formed the study group. They were randomly given either vitamin D3 supplement or placebo. The periodontal parameters, questionnaires and RVG were taken before treatment and post treatment of after 2 months.The inclusion criteriacomprised individuals between the age group of 25-55 years with generalised chronic periodontitis (probing depth of ≥5 mm and clinical attachment loss ≥ 3mm).The exclusion criteria were individuals who had undergone periodontal therapy in the last 6 months with history of any systemic illness such as diabetes, cardiovascular disease, gastrointestinal disturbances or malabsorption syndrome, renal disorder and disorders in bone metabolism. Individuals who are Pregnant, steroid therapy and bisphosphonate therapy were also excluded. Institutional ethical

committee approval was obtained and registration of clinical trial was done.Patients were divided into two groups vitamin D group and placebo group randomly by shuffle of cards method. Vitamin D3 supplement- Commercially available D-rise vitamin D sachets (8 sachets, each containing 1 gram Cholecalciferol- 60,000 IU, given in 8 small boxes for each patient) .The Placebo was - Cellulose powder (8 small boxes for each patient).

Randomisation

III. Results

54 Patients who came to the Department of Periodontology, Sree Balaji Dental College and Hospital and fulfilled the inclusion criteria were analysed for serum 25(OH) 2vitamin D3. Individuals <20ng/ml were included in the study. They were randomly allocated to either vitamin D supplement group or placebo group. Periodontal parameters were assessed. The data were analysed using statistical package for social sciences (SPSS), version 17.0 statistical tools used for analysis include paired t-test. The results indicate a probing pocket depth reduction in the vitamin D supplement group; a post-treatment is 5.3472 compared to 5.7661 in the pre-treatment group. The correlation is 0.667 and the reduction in probing depth is statistically significant ($p<0.002$) [Table I]. Probing pocket depth is greater in the post-treatment, mean value of 7.8033 than in the pre-treatment mean value 5.8033, correlation is 0.813 [Table II]. Statistically significant increase is seen in the post-treatment probing depth ($p<0.001$) [Table III]. Clinical attachment gain in the post-treatment group of mean value 35.61 compared to the pre-treatment mean value 33.72, correlation is 0.858. There is statistically significant gain in the clinical attachment ($p<0.000$) [Table IV]. There is a significant loss of attachment in the placebo group greater in the post-treatment value (mean=44.17) than in the pre-treatment value (mean= 39.67).Association between skin color and vitamin D deficiency indicate that 66.7% of dark skin individuals are vitamin D deficient, showing more deficiency in the dark skin individual which is not statistically significant [Table V] is. A combined intake of fish, diary and egg has less vitamin D deficiency and elimination of diary intake indicates more vitamin D deficiency.[Table VI]. It was noted that more females (73%) are vitamin D deficient compared to males (26.7%).

Table No.1: Table Shows Probing Pocket Depth in Vitamin D Supplement Group

	Mean	N	Std. Deviation	Std. Error Mean	Correlations	Sig. p-value
Pre-treatment	5.7661	18	1.11314	.26237	.667	.002
Post-treatment	5.3472	18	1.69175	.39875		

INFERENCE:
This table shows probing pocket depth reduction in the vitamin D supplement group, post-treatment is 5.3472 compared to 5.7661 in the pre-treatment group. The correlation is 0.667 and the reduction in probing depth is statistically significant (p>0.002).

Graph No 1: Graph showing comparison between pre-treatment and post-treatment probing pocket depth in vitamin D supplement group.

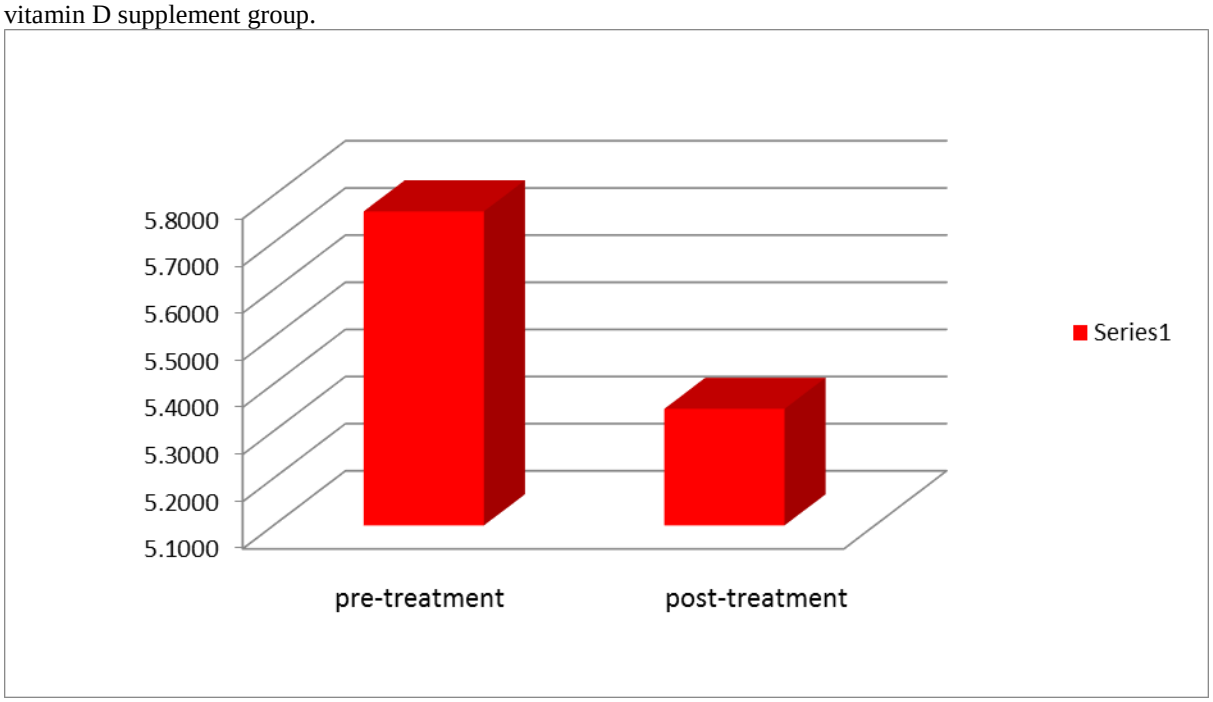


Table No2: Table Shows Probing Pocket Depth in Placebo Group.

	Mean	N	Std. Deviation	Std. Error Mean	Correlations	Sig.
Pre-treatment	5.8033	12	1.74464	.5017	.813	.001
Post-treatment	7.8033	12	1.74067	.50249		

INFERENCE:
This table shows probing pocket depth is greater in the post-treatment, mean value of 7.8033 than in the pre-treatment mean value 5.8033. Correlation is 0.813. Statistically significant increase is seen in the post-treatment probing depth (p>0.001).

Graph No 2: Graph showing comparison between pre-treatment and post-treatment probing pocket depth in vitamin D supplement group.

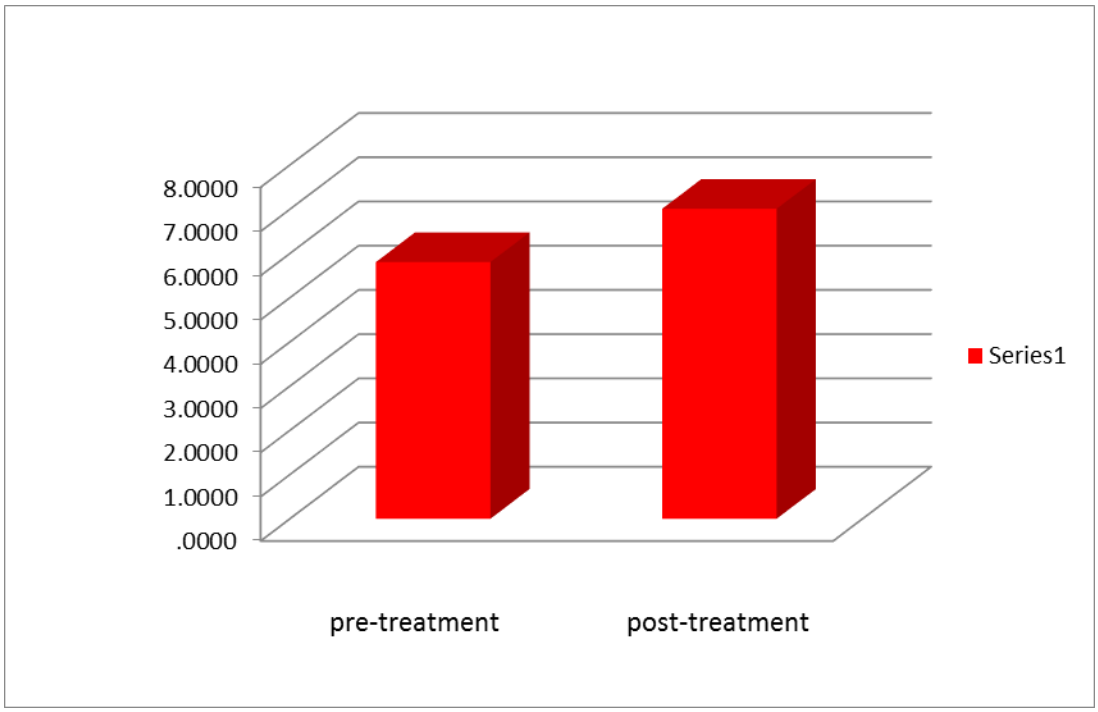


Table No 3: Table Shows Clinical Attachment Level in Vitamin D Supplement Group

	Mean	N	Std. Deviation	Std. Error Mean	Correlations	Sig.
Pre-treatment	35.61	18	9.983	2.353	.858	.000
Post-treatment	33.72	18	8.532	2.011		

INFERENCE:
This table shows clinical attachment gain in the post-treatment group of mean value 35.61 compared to the pre-treatment mean value 33.72. Correlation is 0.858. There is statistically significant gain in the clinical attachment ($p>0.000$).

Graph No 3: Graph showing comparison between pre-treatment and post-treatment clinical attachment level in vitamin D supplement group.

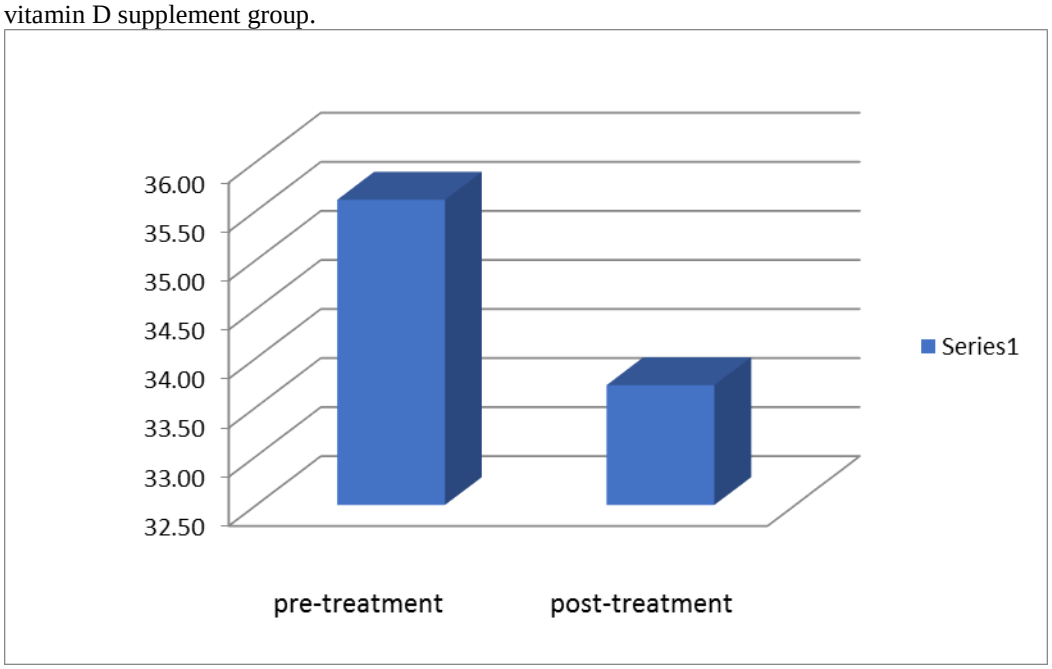


Table No 4: Table Shows Clinical Attachment Level in the Placebo Group

	Mean	N	Std. Deviation	Std. Error Mean	Correlations	Sig.
Pre-treatment	39.67	12	10.731	3.098	.901	.000
Post-treatment	44.17	12	9.183	2.651		

INFERENCE:
This table shows loss of attachment in the placebo group greater in the post-treatment of mean value 44.17 than in the pre-treatment mean value 39.67. The loss of clinical attachment is statistically significant (p>0.000).

Graph No 4: Graph showing comparison between pre-treatment and post-treatment clinical attachment level in placebo group.

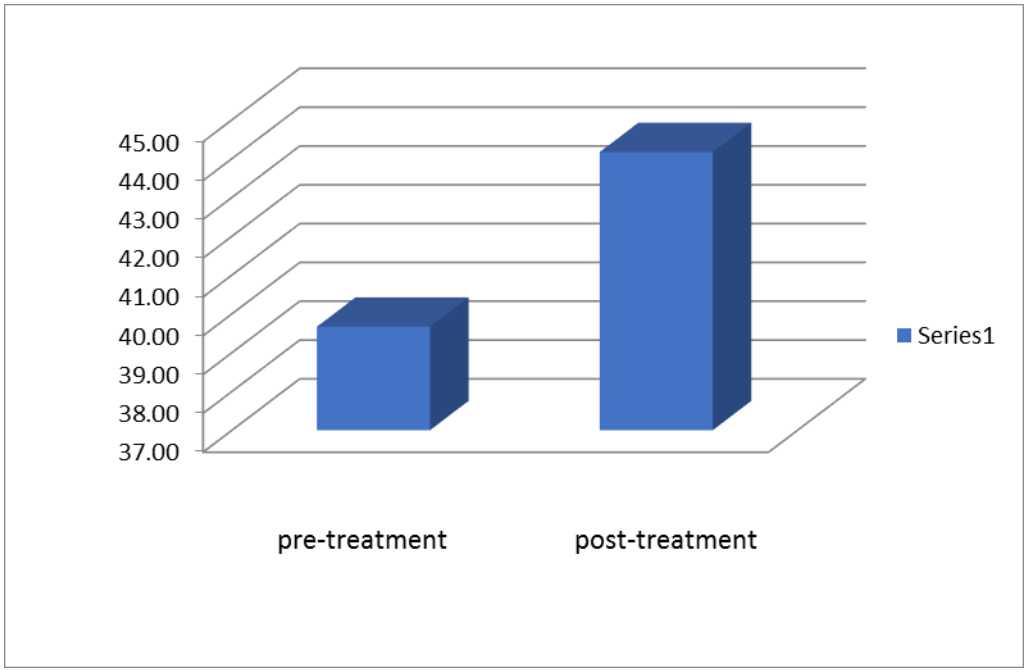


Table No 5: Table Depicting Skin Color and its association with vitamin D deficiency

INFERENCE:
This table shows association between skin color and vitamin D deficiency by Pearson Chi-square test. Skin color ranges from dark to fair. 66.7% of dark skin individuals are vitamin D deficient, showing more deficiency in the dark skin individuals. The association is not statistically significant.

			Vitamin D deficient	Value	P-Value
SKIN COLOR	Dark	Count	20		
		% of Total	66.7%	3.403	.182
	Medium	Count	6	3.555	
		% of Total	20.0%		.169
	Fair	Count	4	.510	.475
		% of Total	13.3%		
Total		Count	30		
		% of Total	100.0%		

Graph No 5: Graph Depicting Association between Skin Color and Vitamin D deficiency

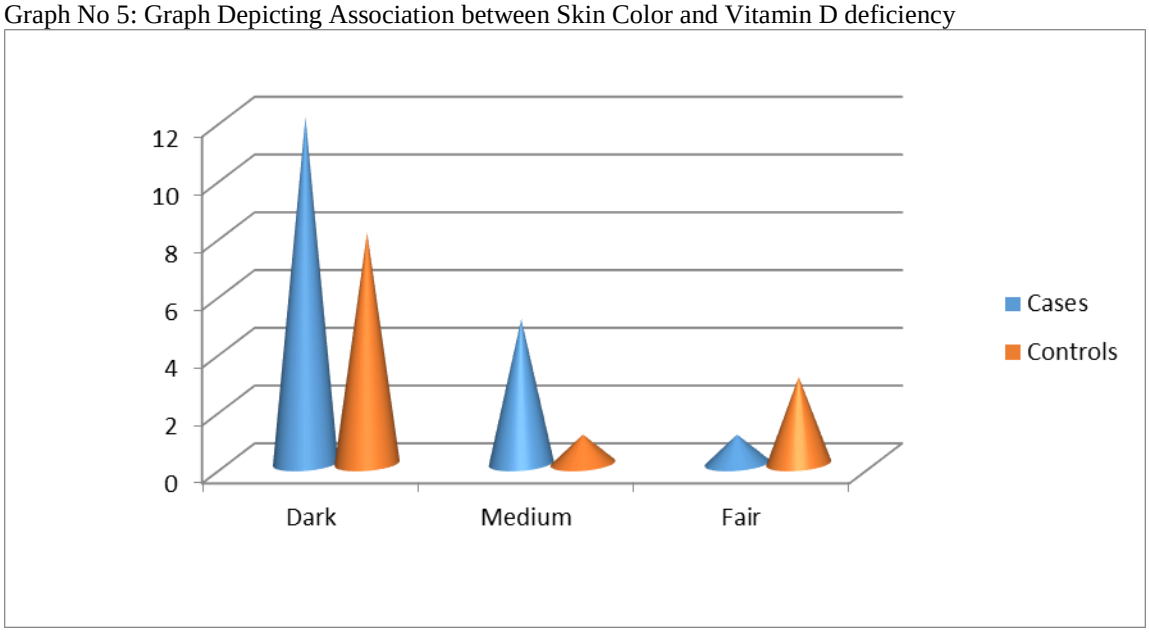


Table No 6: Table Depicting Association Between Foods Taken with vitamin D deficiency

			SUPPLEMENT GIVEN vitamin D/Placebo		
			Cases	Controls	Total
FOODS TAKEN	Nil	Count	1	1	2
		% of Total	3.3%	3.3%	6.7%
	COD, Fish & Egg	Count	1	1	2
		% of Total	3.3%	3.3%	6.7%
	Egg Only	Count	2	1	3
		% of Total	6.7%	3.3%	10.0%
	Fish & Egg	Count	13	7	20
		% of Total	43.3%	23.3%	66.7%
	Fish Only	Count	1	1	2
		% of Total	3.3%	3.3%	6.7%
	Fish, Diary & Egg	Count	0	1	1
		% of Total	.0%	3.3%	3.3%
Total		Count	18	12	30
		% of Total	60.0%	40.0%	100.0%

Chi-Square Tests

	Value	df	p Value
Pearson Chi-Square	1.250[a]	2	.535
Likelihood Ratio	1.243	2	.537
Linear-by-Linear Association	.242	1	.623
N of Valid Cases	30		

INFERENCE:
This table shows that a commonest intake fish, diary and egg of less have vitamin D deficiency. Elimination of diary intake indicates more vitamin D deficiency. The association is not statistically significant.

Graph No 6: Graph Depicting Association Between foods taken and vitamin D deficiency

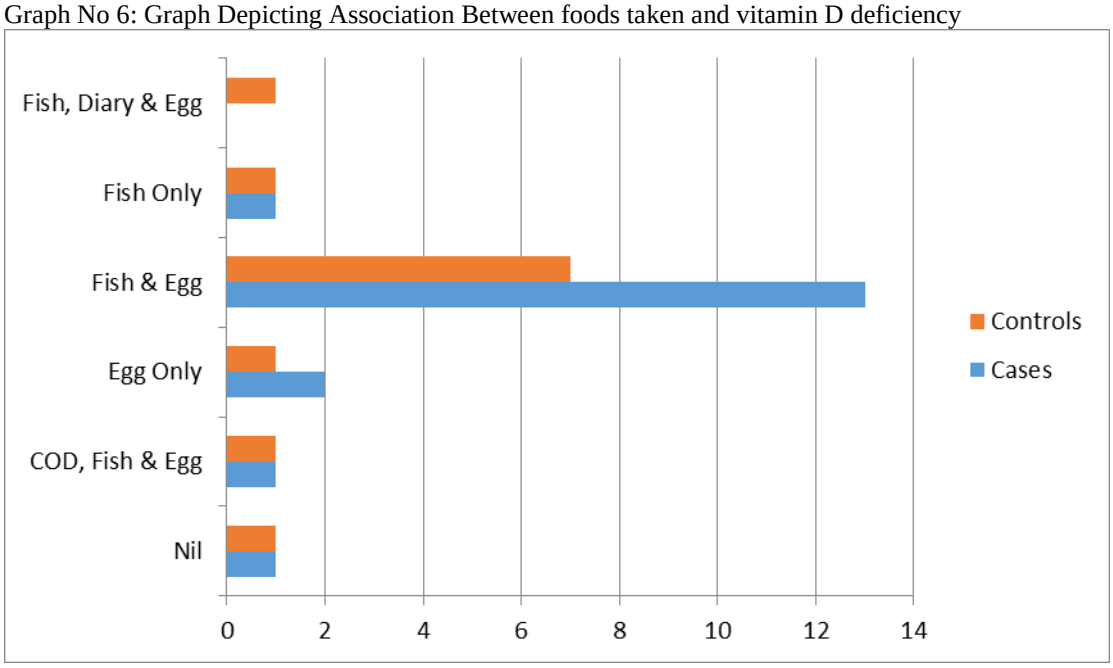


Table No 7: Table depicting association between vitamin D deficiency and gender.

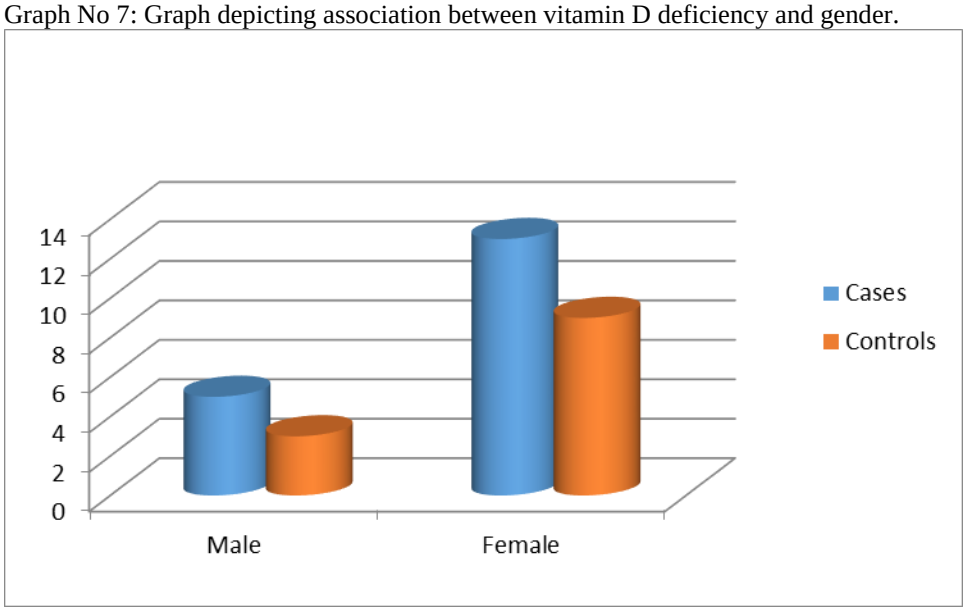
			SUPPLEMENT GIVEN vitamin D/Placebo		
			Cases	Controls	Total
SEX	Male	Count	5	3	8
		% of Total	16.7%	10.0%	26.7%
	Female	Count	13	9	22
		% of Total	43.3%	30.0%	73.3%
Total		Count	18	12	30
		% of Total	60.0%	40.0%	100.0%

Chi-Square Tests

	Value	df	p Value	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.028	1	.866		
Continuity Correction	.000	1	1.000		
Likelihood Ratio	.029	1	.866		
Fisher's Exact Test				1.000	.604
Linear-by-Linear Association	.027	1	.868		
N of Valid Cases	30				

INFERENCE:
This table shows more females are vitamin D deficient. 73.3% of females are deficient compared to 26.7% of males. Correlation is not statistically significant.

Graph No 7: Graph depicting association between vitamin D deficiency and gender.



IV. Discussion

Most epidemiological data suggest that alveolar bone loss is greater in individuals with low bone mass or osteoporosis Hilde bolt CF et al 1997[8], although such an association is not universally accepted (Phipps KR et al 2007). It is likely that low intake of vitamin D and calcium may lead to negative calcium balance, thus causing a secondary increase in calcium removal from bone, including alveolar bone. Such bone loss may contribute to weakening of tooth-attachment apparatus.In addition to its action on skeletal homeostasis, vitamin D and in particular its hormonally active form, 1 α, 25 dihydroxyvitamin D, has anti-inflammatory and anti-microbial effects via modulation of inflammatory cytokine production by immune cells and stimulated secretion of peptides with anti-bacterial action by cells of monocyte-macrophage lineage, Walters MR 1992[16]. These multiple actions of vitamin D are potentially appealing for the management of patients with periodontal disease, whose pathogenesis is based on chronic bacterial driven inflammation. The inflammatory response leads to tissue destruction by direct action of bacterial products or by activation of host defence cells and secretion of inflammatory mediators. These locally produced factors eventually result in connective tissue breakdown and bone loss via activation of osteoclast mediated bone resorption, Page RC 1997[14].

Average vitamin D and calcium intakes in the general population are below current recommendations of 400-600IU and 1,000 to 1,200mg daily, Moore C 2004[11]. Although there is growing consensus that such daily targets are inadequate, and higher vitamin D intakes (800-1,000IU daily) are now recommended by professional organization(National Osteoporosis foundation 2009). It was estimated that 1 billion people worldwide have vitamin D deficiency or insufficiency, Holick MF 2006[7], their potential role in periodontal disease has not been fully determined. A number of studies, Dietrich T 2005[3] suggest that vitamin D and/or calcium intake result in alveolar bone loss, gingival inflammation and/or attachment loss. Most relevant are data on subjects (1,200) enrolled in the Third National Health and Survey (NHANES III), suggesting that lower dietary intake of calcium increased attachment loss in a dose-dependent fashion, Nishida M 2000[13]. In another cohort (6,700 subjects), an association between serum concentrations of 25-hydroxyvitamin D and gingival inflammation was found, possibly linked to vitamin D's anti-inflammatory effect, Dietrich T 2005[3].

A potential role of vitamin D in periodontal health is supported by findings that polymorphisms of the vitamin D receptor gene are associated with periodontitis, alveolar bone, clinical attachment, and/or tooth loss Koji Inagaki I 2003[10]. Thus there is evidence pointing to a potential role of vitamin D and calcium intake on dental health; however, the possible effects of such dietary supplements on periodontal disease parameters and outcomes have not been addressed.

Garcia et al 2011[5] stated that the role of biologically active form of vitamin D in bone and calcium homeostasis demonstrated to function as an immunomodulatory because of its anti-inflammatory effect through inhibition of cytokine production by immune cells and stimulation of monocytes and macrophages to secrete peptides with potent antibiotic activity. This effect of vitamin D has been linked to bacterial-mediated infections, with low levels of vitamin D being associated with increased risk of infectious disease. Therefore vitamin D may be beneficial for the treatment of periodontal disease, an inflammatory condition involving activation of host-defense cells by bacterial release of inflammatory mediators, which results in the destruction of supporting periodontal tissues, including connective tissue and alveolar bone.

In the study done by Al-Zahrani 2006[1], showed an inverse association between the intake of dairy products and prevalence of periodontitis. Controversially, in our study the prevalence of periodontitis was found 3.3% higher in the non-takers of dairy products.Ever since the publication of Hodgkin and colleagues on uncommon prevalence of vitamin D deficient rickets/osteomalacia among Punjabis in India, no studies appeared assessing the vitamin D status of subjects living in tropical and sub-tropical latitude of the India till 1995. Also there has been a prevailing impression among medical professionals that abundance of sunlight prevents vitamin D deficiency in India. However between 1995 and 2000. Kochupillai N 2008[9] showed evidence to show that even doctors and nurses from northern latitude of India have vitamin D deficiency.

These observations are confirmed by other authors for Southern part of the country, Harinarayan CV 2007[6]. These reports thus scientifically establish evidence for prevalence of vitamin D deficiency in the sub-continent, despite abundant light. In our study, 53% of individuals are deficient in spite of living in tropical region. Country-wide preventive intervention, in the form of milk and edible oil fortification with vitamin D would further enhance bone mineral metabolic health in India.

Thomas K. Pilgram 1999[15] studied the relationship between the studies evaluating the relationship between longitudinal changes in radiographic alveolar bone height in relation to periodontal disease. They found weak correlations between changes in alveolar bone height. This is similar to our study, where we evaluated the changes in the alveolar crestal bone height before and after treatment. It showed a positive correlation of increase in the crestal height of alveolar bone.In the study done by, Garcia 2011[5] showed clinical parameters improvement on vitamin D and calcium supplements for one year. In addition to its well-known activity in preventing rickets and osteomalacia, 1, 25 (OH) $_2$D3 has been shown to have important anticancer, immune modulatory and innate immune effects, through VDR activation. The 1, 25 (OH) $_2$D3-VDR system plays a role in oral homeostasis and its dysfunction may lead to periodontal disease. Vitamin D research should make important contribution to oral medicine.

The results of this study indicate a probing pocket depth reduction in the vitamin D supplement group. The post-treatment pocket depth is 5.3472 compared to 5.7661 in the pre-treatment group. A correlation of 0.667 and statistically significant ($p<0.002$) reduction in pocket depth is noted. Clinical attachment gain in the post-treatment group was 35.61 compared to the pre-treatment mean value 33.72 indicating a statistically significant gain in the clinical attachment ($p<0.000$).This was in accordance with the study done by Garcia in 2011, where they concluded that improvement in the periodontal parameters (probing pocket depth, clinical attachment, gingival index, bleeding sites) was found significant ($p<0.0001$) in the vitamin D and calcium supplement takers than in the non-takers. This study also recorded an increase in probing depth and loss of attachment post treatment in the placebo group compared to pre-treatment values indicative of a progression of periodontitis as vitamin d deficiency persisted. Radiographic findings reveal a gain in crestal bone height in the vitamin D supplement group compared to the placebo where there were no changes. This was found in accordance with the study done by D Douglas Miley in 2009[4], where they concluded that vitamin D supplement and calcium in takers showed a borderline significance improvement in the crestal alveolar bone height.

Skin color has many reviews regarding its influence on cutaneous vitamin D synthesis. Takiwaki H in 1998, Webb AR in 2006[17] proved that the cutaneous vitamin D synthesis decreases with age. Skin color can be estimated subjectively by the observers using color scale. In our study the association between skin color and vitamin D deficiency shows that as the skin color ranges from dark to fair percentage of vitamin D deficiency decrease from 66.7% to 3.3% although the association is not statistically significant. This is reinforced by the study done by Catherine A Mc Carty in 2008[2], where they found that sunlight exposure and vitamin D concentration was not particularly high due to various factors affecting cutaneous vitamin D synthesis.The combined intake of fish, diary and egg resulted in lesser deficiency values compared to individuals consuming only eggs/fish. Elimination of diary intake indicates more vitamin D deficiency. In our study the association found is not statistically significant. This is in accordance with the study done by Al-Zahrani[1] in 2006, in which he found an inverse association between intake of dairy products and prevalence of periodontitis.

Another notable finding was that females were more vitamin D deficient (73.3%) compared to males (26.7%). The association was not statistically significant. The probable explanation could be that in a conservative society like ours women tend to stay more indoors with less exposure to sunlight. In our study there was no prevalence of vitamin D deficiency between the months of March and June.Similar facts was emphasized by Levis S in 2005 that vitamin D deficiency exist for those who avoid sunlight, living indoors and residing in the sub-tropical lattitude. The patients who were takers of vitamin D supplements general showed good compliance and improved in their general health status.

V. Summary and conclusion

Vitamin D deficiency is endemic and associated with numerous serious diseases. Understanding the physiology of vitamin D and having a high index of suspicion are keys to making effective diagnosis. Periodontal disease results in the production of proinflammatory cytokines, which also result in osteoclastogenesis. It follows that alveolar bone in patients with periodontal disease and low levels of vitamin D and calcium should be under a heavier osteoclastic load. Periodontal disease's unique microbial aetiology, hard tissue environment, it may be that the effect of vitamin D and calcium on alveolar bone is more pronounced. Perhaps a new era in medicine, the vitamin D era is on the rise. Although the existence, depth and breadth of any vitamin D era remain to be seen, a burgeoning literature points to horizons beyond our vision.

References

[1]. **Al-Zahrani.** Increased intake of dairy products is related to lower periodontitis. J Periodontol. 2006;7(2):289-94.

[2]. **Catherine A McCarty.** Sunlight exposure assessment: Can we accurately assess vitamin D exposure from sunlight questionnaires? Am ClinNutr 2008;87:1097S-101S.

[3]. **Dietrich T, Nunn M, Dawson-Hughes B.** Association between serum concentrations of 25-hydroxyvitamin D and gingival inflammation. Am ClinNutr 2005;82:575-580.

[4]. **Douglas Miley, Nathalia Garcia, Charles F.Hildebolt**. Cross-sectional study of vitamin D and calcium supplementation effects on chronic periodontitis. J Periodontol 2009;80:1433-1439.

[5]. **Garcia, Charles F. Hildebolt, Douglas Miley.** One-year effects of vitamin D and calcium supplementation on chronic periodontitis. J Periodontol 2011;82:25-32.

[6]. **Harinarayan CV, Ramalakshmi t, Prasad UV.** High prevalence of low dietary calcium, and vitamin D deficiency in healthy south Indians. Am J Clin Nutr 200;85(4):1062-77.

[7]. **Holick MF.** High prevalence of vitamin D inadequacy and implications of health. Mayo ClinProc 2006;81:353-73.

[8]. **Hildebolt CF, Sidney H. mStein.** Vitamin D and its impact on oral health- An update. J of the Tennessee dental association 1997;29:91-2.

[9]. **Kochupillai N.** The physiology of vitamin D: Current concepts. Indian J Med Res 2008;127:256-262.

[10]. **Koji Inagaki, Elizabeth A. Krall, James C. Fleet**. Vitamin D receptor alleles, periodontal disease progression and tooth loss in VA dental longitudinal study. J Periodontol 2003;74:161-167.

[11]. **Moore C, Murphy MM, Keast DR.** Vitamin D intake in the United States. J Am Diet Assoc 200;10:9980-3.

[12]. **Nathalia Garcia, Charles F. Hildebolt, Douglas Miley.** One-year effects of vitamin D and calcium supplementation on chronic periodontitis. J Periodontol 2011;82:25-32.

[13]. **Nishida, Sara G. Grossi, Robert G. Dunford.** Calcium and the risk for periodontal disease. J Periodontol 2000;71:1057-1066.

[14]. **Page RC, Kornman KS.** The pathogenesis of human periodontitis: An introduction. J Periodontol 1997;1:9-11.

[15]. **Thomas K. Pilgram, Charles F. Hildebolt, Naoko Yokoyama.** Relationship between longitudinal changes in radiographic alveolar bone height and probing depth measurements. J Periodontol 1999;70:829-823.

[16]. **Walters MR.** Newly identified actions of vitamin D endocrine system. Endocr Rev 1992;13:719-764.

[17]. **Webb AR.** Who, what, where and wwhen-influences on cutaneous vitamin D synthesis. Prog Biophys Mol Biol 2006;92(1):17-25.