ORIGINAL RESEARCH PAPER

Dermatology

A STUDY ON THE CORRELATION OF SERUM CHOLECALCIFEROL LEVEL AND VITILIGO

KEY WORDS:

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ABSTRACT

Background: Vitamin D is a harmone known to play a major role in melanogenesis. Vitiligo can be associated vitamin D deficiency. Treatment outcomes can be better with vitamin D supplements and phototherapy along with other treatment modalities by identifying vitiligo patients with serum cholecalciferol deficiency. **Aims:** To study the correlation between serum cholecalciferol levels and vitiligo with respect to type, duration and severity. **Methods:** (including settings and design and statistical analysis used) This is a hospital based case control study with a sample size of 180 which includes 120 cases and 60 controls. The study was done for 6 months from December 2016 to May 2017 in dermatology department. Clinically diagnosed vitiligo patients constitute the cases. Age matched and sex matched healthy volunteers comprised the control group. Ethical committee approval was obtained. Informed consent was obtained from all those who were included in this study. Detailed history and examination was carried out and recorded. The patients were categorized based on the type, duration, and severity (VASI score) of vitiligo. Serum 25-OH cholecalciferol levels were calculated using Euro immune ELISA kit. The results were compared. **Results:** Cholecalciferol deficiency was commonly associated with vitiligo vulgaris and universalis, severity with VASI score of >26% and a disease duration of >5 years. Some of these patients had normal values which was attributed to phototherapy. **Limitations:** This study did not compare the improvement of vitiligo after vitamin D supplementation in those who had deficiency. **Conclusions:** Thus in this study, there is a significant correlation between serum cholecalciferol and the type, duration and severity of vitiligo. Those patients receiving phototherapy showed normal cholecalciferol and were improving clinically.

INTRODUCTION:

Vitiligo is an autoimmune pigmentary disorder caused by destruction of functional melanocytes in epidermis and infundibulum of hair, characterized by depigmented patches or macules.[1] It affects both sexes and all races equally. The inheritance is polygenic or autosomal dominant with variable penetrance. Vitamin D is synthesized from 7 dehydrocholesterol present in skin which is converted to 25(OH) cholecalciferol and then to its active metabolite 1,25(OH)2cholecalciferol and has a role in skin pigmentation. Vitamin D in addition to its regulatory effect in calcium and bone metabolism, controls cell proliferation and differentiation, exerts immuno regulatory activities via its nuclear receptor and increases melanogenesis. It increases the tyrosinase content of cultured human melanocytes by its antiapoptotic effect.[2] Topical vitamin D increased L-3,4 dihydroxyphenylalanine positive melanocytes[2] and is used in combination with other modalities of treatment for vitiligo successfully. Vitamin D exerts immunomodulatory effect by inhibiting the expression of cytokines IL6, IL8, IL10, IL12, IF, TNF[3-5] which are pro inflammatory and proapoptotic in vitiligo. Another study revealed Apa-I polymorphism[5] of vitamin D receptor gene to be associated with vitiligo. Normal serum vitamin D is 30-70ng/ml (75- 250 nmol/L). Low levels of vitamin D has been observed in vitiligo and other autoimmune disorders.[2-5] The improvement of serum vitamin D deficiency after UV exposure correlates with clinical improvement[6] as assessed by VASI score.[7] Thus, vitamin D and its receptor play a role in etiopathogenesis of skin pigmentation. Hence, we decided to study on this association among vitiligo patients with respect to type, duration and severity.

METHODS:

This is a hospital based case control study with a sample size of 180 including 120 cases and 60 controls. The study was done for 6 months from December 2016 to May 2017 in dermatology department in tertiary care hospital in south India. Clinically diagnosed cases of vitiligo attending dermatology department comprised the cases. Age matched and sex matched healthy volunteers comprised the control group. Ethical committee approval was obtained. Informed consent was obtained from all those who were included in this study. All were interrogated for a detailed history and a meticulous examination of each case was carried out and recorded in a proforma separately for cases and controls. History of precipitating factors such as trauma, chemicals, stress, and other associations were specifically asked for and noted. History suggestive of thyroid disease, atopy, diabetes was noted. A complete general physical examination was done in all those who were included in the study. A thorough systemic examination was also made for associated disorders and the findings were noted. Detailed dermatological examination including the mucosa was carried out to classify the disease, to know the extent of vitiligo and to study the specific features such as trichrome, quadrichrome, and leukotrichia. All those who were included in this study were subjected to the following investigations: complete hemogram, blood sugar, renal function test, liver function test, serum fasting lipid profile, serum proteins, antinuclear antibody, and serum 25 hydroxy cholecalciferol.

The patients were categorized based on the clinical type, duration, and severity of vitiligo. The patients were clinically classified as: Focal, segmental, mucosal, acrofacial, vitiligo vulgaris and vitiligo universalis. The patients were categorized on the basis of duration as follows: 0-5 years, 6-10 years, 11-15 years, 16-20 years and >21 years. Severity of vitiligo was assessed using VASI score and were categorized as follows: 0-10%, 11-25%, 26-50%, 51-75% and 76-100%. Serum 25-OH cholecalciferol levels were calculated using Euro immune ELISA kit. The cases and controls were categorized based on serum 25 OH cholecalciferol levels as follows: Very severe deficiency (<5 ng/ml), Severe deficiency (5-10 ng/ml), Deficiency (10-20 ng/ml), Sub optimal (20-30 ng/ml), Normal (30-50 ng/ml), Upper normal (50-70 ng/ml), Above normal (70-150 ng/ml), Intoxication (>150 ng/ml).

Results: This study comprises of 120 cases and 60 controls which included 26 cases and 13 controls in the age <20 years, 43 cases and 23 controls in 21-40 years, 43 cases and 21 controls in 41-60 years, 8 cases and 3 controls in >60 years. There were 59 males and 61 females among cases and 29 males and 31 females in controls. Thus the age (P value- 0.968)

and sex (P value- 0.916) of cases and controls were matched. Serum cholecalciferol levels are compared between cases and controls in table 1. In order to avoid confusion, those people with very severe (<5 ng/ml) and severe deficiency (5-10 ng/ml) of cholecalciferol levels were clubbed together as severe deficiency which includes 31 cases and 4 controls. Those with deficiency (10-20 ng/ml) and suboptimal levels (20-30 ng/ml) of serum cholecalciferol were clubbed together as deficiency which includes 67 cases and 30 controls and those with serum cholecalciferol >30ng/dl were clubbed together as normal with 22 cases and 26 controls. The correlation of serum cholecalciferol among various types of vitiligo is compared (p value- 0.025) in chart 1, correlation with the duration of vitiligo is compared (p value- 0.001) in chart 2 and the correlation with the severity of vitiligo is compared (p value- <0.001) in chart 3.

Discussion: Out of the total 180 people included in this study, 120 were vitiligo cases and 60 were age and sex matched controls. Indian case control study done by Prakash D et al,[8] 45 cases and 45 age and sex matched controls were compared. In another Iranian study,[9] 30 cases were compared with 30 age and sex matched controls. In a Turkish study by Karagun E.,[10] 50 vitiligo patients and 47 controls were compared. In another Turkish study by Takci Z., [11] 44 vitiligo vulgaris patients were compared with 43 controls. Thus, this study included more number of cases and controls when compared with other studies.

The age of cases and controls were matched with a p value of 0.968. The mean age of cases is 37.6 $\pm$ 17.2 and that of controls is 36.2$\pm$15.8. In the Indian case control study done by Prakash D et al,[8] mean age of patients was 43.78 $\pm$ 14.70 SD. In the Iranian study,[9] the mean age was 30.2 $\pm$ 0.91 in cases and 34.76 $\pm$ 1.07 in controls. In the study by Karagun E.,[10] the mean ages of the patient and control groups were 30.96 $\pm$10.57 and 31.45 $\pm$8.33 years, respectively. In the study by Takci Z.,[11] a total of 44 patients with mean age of 34.5 $\pm$ 16.1 years (range: 16–60 years) and 43 controls with mean age of 33.0 $\pm$ 12.6 years (range: 17 – 60 years) were included in the study.

In this study, out of the 120 cases, 59 were males and 61 were females and out of the 60 controls included 29 were males and 31 were females. Thus, the sex of cases and controls are matched with a p value of 0.916. In the study done by Prakash D et al,[8] out of 45 cases, 26 were male and 19 were female, with a male: female sex ratio of 1.5:1. In the Iranian study,[9] 60 cases comprised of 32 males (53%) and 28 females (47%). In the study by Karagun E.,[10] 28 (56%) males and 22 (44%) females were included in the study group. The control group consisted of 30 (63%) males and 17 (37%) females. In the study by Takci Z., [11] 44 cases included 20 females and 24 males while 43 controls included 33 females and 10 males. Thus the genders in this study are matched equally like that of the other studies. This study shows preponderance of vitiligo vulgaris (45%) which is in accordance with other studies. Focal, mucosal and universal vitiligo were commonly seen in females (41%) while segmental and acrofacial vitiligo were commonly seen in males (32.2%) in this study. In the study done by Prakash D et al,[8] there were 53% patients with vitiligo vulgaris type. In the study by Karagun E.,[10] all the patients belonged to generalised vitiligo. In the study by Takci Z., [11] 6.8% had localized vitiligo and 93.2% had the generalized.

Majority (80.83%) of the patients included in this study are affected by vitiligo for <5 years duration. This is in accordance with other study done by Prakash D et al,[8] where 75.55% cases had vitiligo for <5 years.

All the patients with normal values and above normal value had been treated with phototherapy and the values were attributed to the same. They showed clinical improvement also. Serum cholecalciferol was low in cases (81.6%) compared to controls (56.7%). Thus significant correlation exists between vitiligo and cholecalciferol. (P value<0.001) But, in the study done by Prakash D et al,[8] there were no difference in serum cholecalciferol levels between cases and controls. In the Iranian study,[9] cholecalciferol levels were lower in cases (Mean$\pm$S.D. 10.24$\pm$1.72) than controls (Mean$\pm$S.D. 18.31$\pm$7.39). In the study by Karagun E.,[10] the patients' serum vitamin D levels ranged from 6 to 42 ng/ml (mean: 12.04 $\pm$8.84 ng/ml); in the control group they ranged from 8 to 39 ng/ml (mean: 12.91 $\pm$6.08 ng/ml). The patients had lower circulating vitamin D levels than controls, but this difference was not significant (p = 0.570). In the study by Takci Z., [11] 72.73% of the cases and 30.2% controls had deficiency. Thus, our study is in accordance with the study done by Tackci Z.

Though all the patients of all the vitiligo types with severe deficiency and deficiency outnumbers those having normal values of cholecalciferol, this study showed exclusively deficiency and severe deficiency with vitiligo vulgaris (36.66%) and universalis (5.83%) which implies a significant correlation (P value- 0.025) with the type of vitiligo. Ten persons (18.5%) with normal values in vitiligo vulgaris were under phototherapy and are clinically improving. But, in the study done by Prakash D et al,[8] there is no change in cholecalciferol levels with the type of vitiligo.

Among patients with vitiligo for > 5 years duration, only 5 showed normal values and all these patients were under phototherapy and were having clinical improvement. Majority of the patients were suffering from vitiligo for <5 years duration, majority (80) had deficiency and severe deficiency while only 17 had normal cholecalciferol values. Thus, this study shows significant correlation (P value-0.001) with duration of vitiligo. But, in the study done by Prakash D et al,[8] there is no change in cholecalciferol levels with the duration of vitiligo.

In VASI score >26%, none of them show normal values, except 2 (9.1%) who were under phototherapy were clinically improving. This study shows significant correlation (P value<0.001) with the severity of vitiligo. But, in the study by Takci Z., [11] there was no change in cholecalciferol levels with the severity of vitiligo patients.

In both cases and controls, serum cholecalciferol show some improvement with age since severe deficiency is less common in >40 years of age suggesting significant correlation with age. (P value-0.041 for cases and 0.002 for controls). This indirectly shows the minimal sun exposure among younger age groups and higher outdoor activities in older age group. Moreover, phototherapy (PUVA) is started in >18 years of age. In the study done by Prakash D et al,[8] there is no change in cholecalciferol levels with the age of vitiligo patients. In the study by Karagun E.,[10] there is no change in cholecalciferol levels with the age of vitiligo patients. In the study by Takci Z.,[11] there is no change in cholecalciferol levels with the age of vitiligo patients. None of the studies compared age of the controls with cholecalciferol.

In both cases and controls, there is no sex prediliction (P value- 0.191 for cases and 0.131 for controls) for serum cholecalciferol in normal and deficient groups, though females show a greater preponderance to severe deficiency. In the study done by Prakash D et al,[8] there is no change in cholecalciferol levels with the sex of vitiligo patients. In the Iranian study,[9] Male patients had lower levels of vitamin D compared to controls (7.25 ng/ mL vs. 13.31ng/mL, P=0.03) while no significant difference was observed between female patients and controls (14.12 ng/mL vs. 16.25 ng/mL, P=0.51). In the study by Karagun E.,[10] there is no change in cholecalciferol levels with the sex of vitiligo patients. In the study by Takci Z.,[11] there is no change in cholecalciferol levels with the sex of vitiligo patients. None of the other studies compared cholecalciferol variation in sex of control group.

In both cases and controls, normal serum cholecalciferol levels were seen more commonly in those exposed to UV rays compared to those who are not exposed. Significant correlation is seen in cases with P value of <0.001 but the association is not significant in control group with P value-0.073.

The fact that the patients under phototherapy showed clinical improvement following phototherapy supports the role of vitamin D in the pathogenesis of vitiligo. There is no case control study that assessed cholecalciferol levels with UV exposure. But, this study is in accordance with the study done by Sehrawat et al[12] and the study done by Danilo et al[13] where they have compared cholecalciferol with UV exposure. None of the other studies compared UV exposure of controls with cholecalciferol.

Limitations:

This study did not compare the results after vitamin D supplementation.

CONCLUSION:

In this study, there is a significant correlation between serum cholecalciferol and vitiligo. There is also significant correlation of cholecalciferol with the clinical type, duration and severity of vitiligo.

The study showed deficient cholecalciferol levels in vitiligo vulgaris and universalis, with vitiligo of longer duration and of VASI score >26%. Those patients receiving phototherapy showed normal cholecalciferol and were improving clinically. The observation made in this study favours the role of low vitamin D level in the pathogenesis of vitiligo and the role of vitamin D supplementation in the management of vitiligo.

Key Messages:

This study compared the correlation of serum cholecalciferol with the type, duration and severity of vitiligo by which the vitiligo patients who are in need of vitamin D supplements along with other treatment modalities can be identified.

Tables:

Serum VIT D3(ng/ml)	Group	
	cases	controls
Very severe deficiency(< 5)	9 (7.5)	1 (1.7)
Severe deficiency(5.1-10)	22 (18.3)	4 (6.7)
Deficiency (10.1-20)	39 (32.5)	17 (28.3)
Suboptimal (20.1-30)	28 (23.3)	12 (20.0)
Normal (30.1-50)	17 (14.2)	17 (28.3)
Upper normal (50.1-70)	4 (3.3)	9 (15.0)
Above normal (>70)	1 (0.8)	0
Total	120 (100.0)	60 (100.0)
Mean±SD	19.8±13.6	29.5±17.1
Min, Max	2.1, 82.0	4.7, 69.4
P value	< 0.004 Significant	

Illustrations:

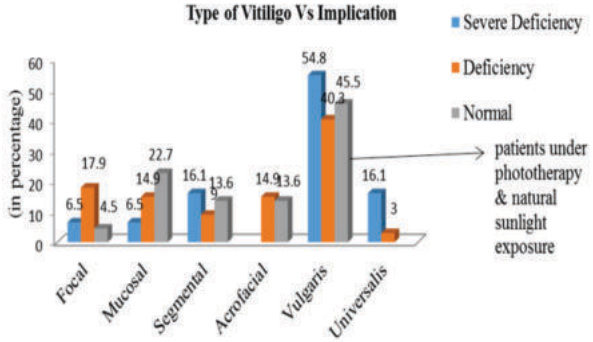


Chart 1: Comparison of serum cholecalciferol among various types of vitiligo

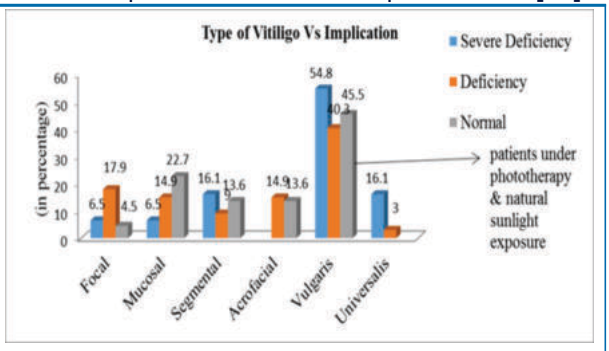


Chart 2: Comparison of serum cholecalciferol with the duration of vitiligo

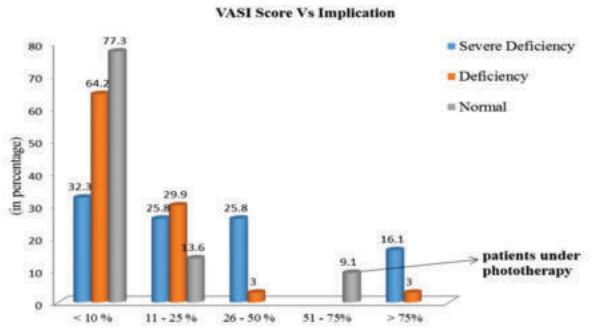
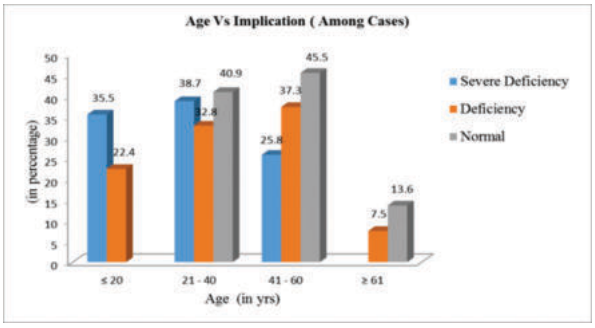


Chart 3: Comparison of serum cholecalciferol with the severity of vitiligo



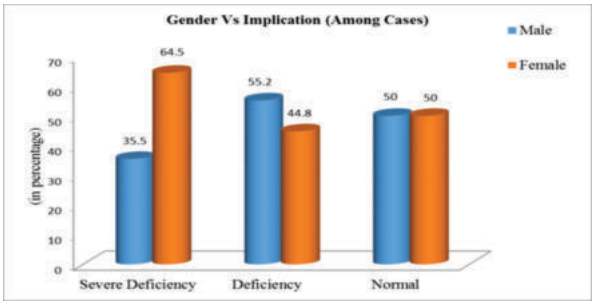


Chart 4 and 5: Comparison of serum cholecalciferol with the age of cases and controls respectively

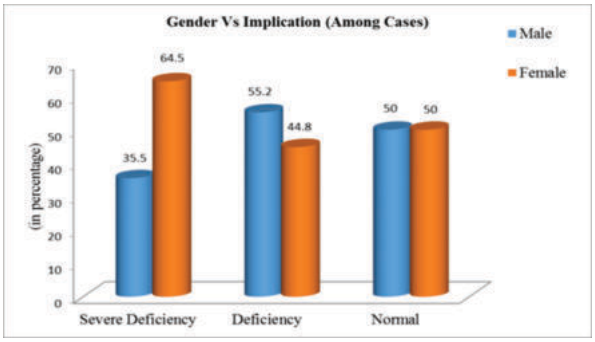


Chart 6 and 7: Comparison of serum cholecalciferol with the sex of cases and controls respectively

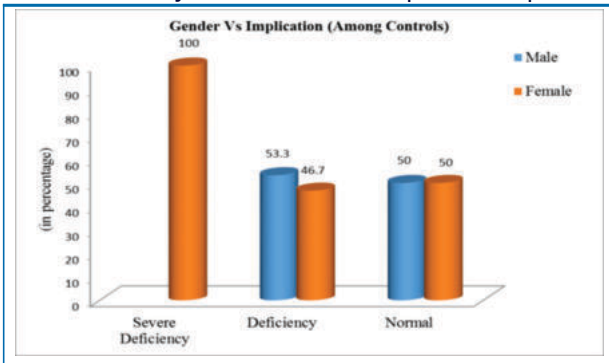


Chart 7

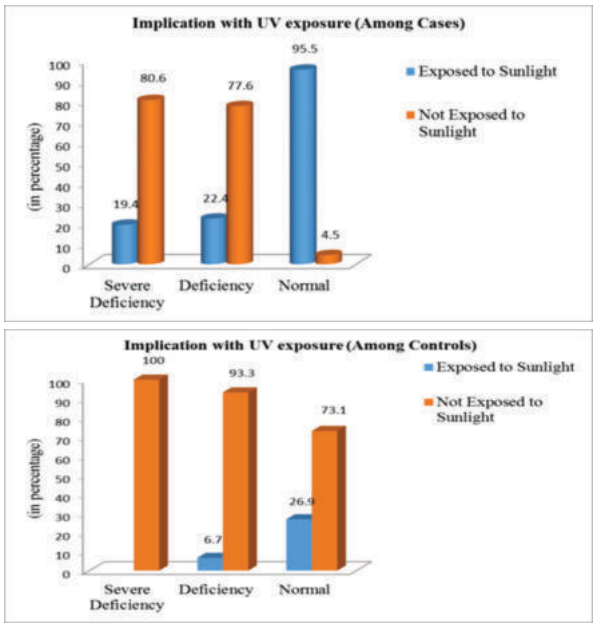


Chart 8 and 9: Comparison of serum cholecalciferol with sun exposure

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