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A STUDY OF EPIDEMIOLOGICAL, ETIOLOGICAL AND CLINICAL FACTORS IN HYPER-PIGMENTATION POPULATION IN NORTH GUJARAT

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Keywords:

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ABSTRACT: Background: Hyperpigmentation (HP) is a common dermatological disease. Indian population presents in a variety of dermatological pigmentation. Effects of Nutrients and metabolites factor are important for skin hyperpigmentation condition. **Aims and Objectives:** In this study, we aimed to evaluate the status of Haemoglobin, vitamin B12, Ferritin, and TSH levels in people with hyperpigmentation from a different region of Aravalli district Gujarat, India. **Materials and Method:** A study based retrospective, prospective and Multi-centric study conducted at the dermatological outpatient clinics at Modasa, Vatrak, Ranasanarea of Aravalli district, Gujarat, India. In this, we studied a total of 70 hyperpigmented patients fulfilling with inclusion criteria. Hyperpigmentation patients correlate with serum vitamin B12; Ferritin, CBC, and TSH during a four-year period from June 2015 to May 2019 were included in the study. Those were diagnosed with following various examinations and tests. A detailed examination was performed with respect to skin hyperpigmentation. Clinical and laboratory data compare with normal control. Student t-test used for statistical analysis. **Results:** A total of 70 HP patients were investigated with age group in between 11 to 40 years (mean age of 26.49 ±10.08). We observed common features were dark skin coloration on face, neck, elbow, knee, surround to eyes, on fingers, etc. HP Patients showed serum Haemoglobin level (Mean ± SD, 11.81 ± 2.414) (P value 0.0016 < 0.005). Patient's showed the vitamin B12 level in the HP group (Mean ± SD, 293.4 ± 137.2). It is non-significant. The serum ferritin level in the HP group (Mean ± SD, 44.04 ± 101.7)(P value 0.0072 < 0.005). TSH level showed below normal [<3.0 miu/ml], 03 [7.69%] showed TSH level above Normal range [0.3 to 5.0 miu/ml] and others 35 [89.74 %] showed in normal range (P > 0.005). **Conclusion**: Skin Hyperpigmentation due to Nutrients and metabolic factors. Serum level of ferritin and Haemoglobin were a significant role in hyperpigmentation conditions, but vitamin B12 played a non-significant role in hyperpigmentation in north Gujarat.

INTRODUCTION: Hyperpigmentation (HP) is a common dermatologic problem that may have a significant impact on the patient's appearance and quality of life [1, 2].

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The irregularity of constitutive pigmentation around the world is well-established, particularly in Asian and Indian subjects [3].

Common Hyperpigmentary skin condition observed in human population likes, post-inflammatory hyperpigmentation [4], melasma [5], nevus of ota [6], Maturational hyperpigmentation [7], Perioral hyperpigmentation [8], Exogeneous ochonosis [9], Dermatosis Papulosa Nigra [10], Acquired melanocytic nevi [11], Lichen planus pigmentosus [12], Ephelids [13], Peri-orbital melanosis

[14], Seborrheic keratosis [15], Acanthosis Nigricans [16] *etc*. Human skin presents in a variety of common pigmentary conditions depending on various environmental factors, nutritional, metabolic causes, and some medications [17]. It also depends on Genetics, Physiological, Physical, endocrine, inflammation, systemic diseases, infective, post-inflammatory, pregnancy, and miscellaneous [18]. Many forms of hyperpigmentation are caused by an excess production of melanin [19-20].

Nutritional factors are significant for skin conditions [21]. The influences of vitamins, carotenoids, and polyunsaturated fatty acids on skin condition [22]. Normallystudied antioxidants such as carotenoids, tocopherols, and flavonoids, as well as vitamins (A, C, D, and E), essential omega-3-fatty acids, some proteins, and lactobacilli, have been referred as agents capable of promoting skin health and beauty [23]. Skin diseases may lead to metabolic imbalances and cause nutritional deficiencies [24].

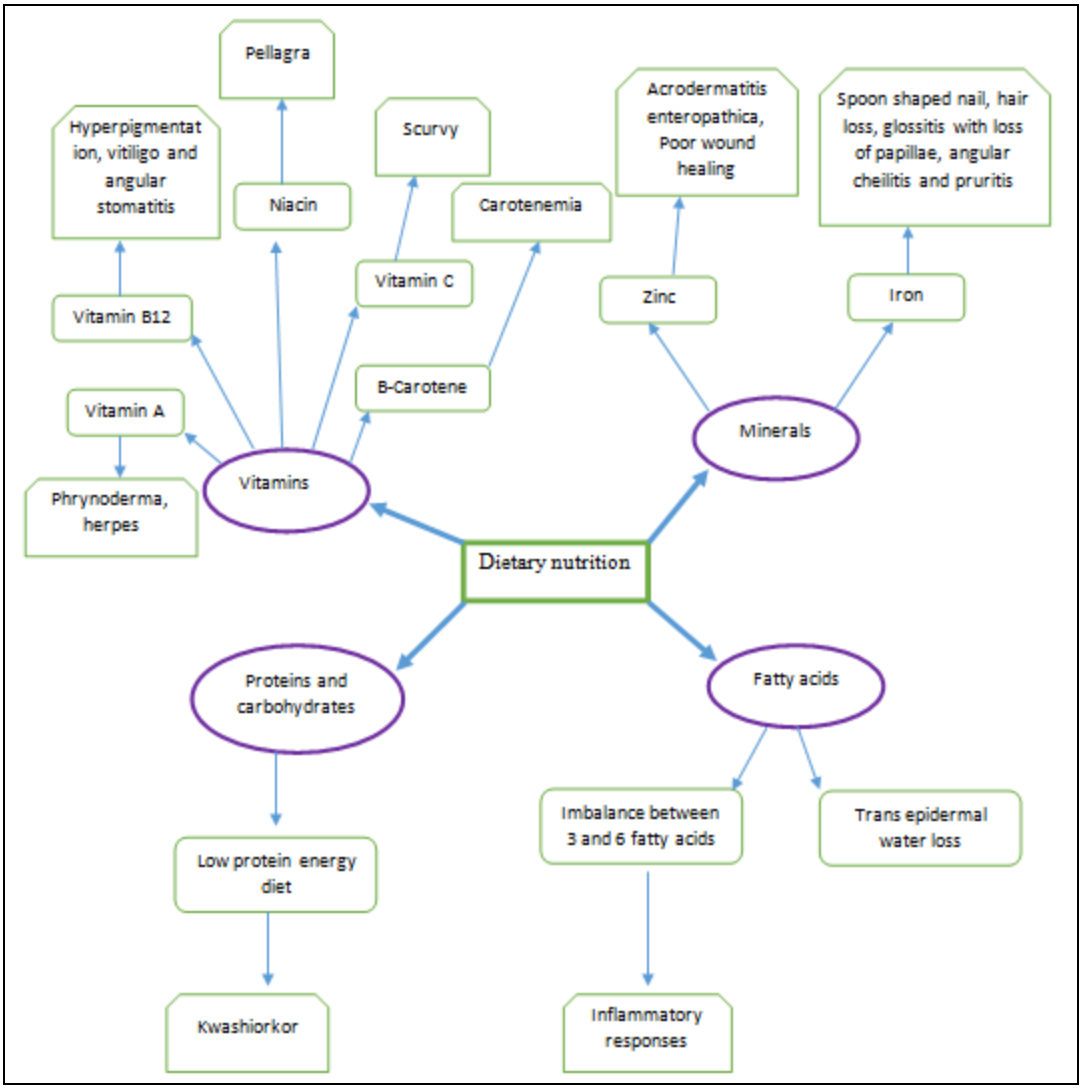

CHART 1: DIFFERENT DERMATOLOGICAL CONDITION DUE TO NUTRIENTS DEFICIENCY

Cutaneous manifestations associated with vitamin B12 deficiency are skin hyperpigmentation, vitiligo, angular stomatitis, and hair changes [25-27].

Peri-orbital hyperpigmentation was laboratory investigation including complete blood count, vitamin B12 level, and thyroid profile is done[28]. Serum ferritin may be a good indicator of susceptibility to post-sclerotherapy pigmentation [29].

Nutrition and metabolites, its effects on skin has always been an interesting topic for scientists, researcher, and physicians throughout the worldwide.

According to the review literature, vitamin B12, ferritin, CBC, and TSHcorrelation with hyperpigmentation we cannot get the proper information from Aravalli district, Gujarat, India.

In this manuscript, we describe the association and the role of vitamin B12, Ferritin, Haemoglobin, and TSH in hyperpigmentation of the skin. This study has been conducted with the aim of looking into the Aetiology, pathogenesis and clinical profile in patients with Hyperpigmentation.

MATERIALS AND METHOD: A Total number of 70 hyperpigmentation patients (males 28 and females 42) and 22 normal controls (17 males and 5 females) were included in this study. This study was conducted in dermatology OPD practice at clinicsin Aravalli district (Modasa, Vatrak, Ranasan), Gujarat, India. The prospective, retro-spective, observational, and multi-centric study was carried out during a four-year period from June 2015 to May 2019 on successive patients with a diagnosis of hyperpigmentation enrolled in our study. An understood informed consent was obtained from all the patients that participated in the study. A structured interview assisted questionnaire was used to collect the biodata (Age, Sex, weight, and height). The ethical approval was given by Human Institutional Ethics committees (IEC) at Shri Sarvagenic pharmacy college, Mahesana. (Ref. SCREC/2019-20/07). The diagnosis of hyperpigmentation by laboratory evaluation of blood serum level of Vitamin B12, CBC, ferritin, and TSH. Serum vitamin B12 level was assessed by radioimmunoassay and low serum vitamin B12 levels (Normal range < 211 pg/ml). Haemoglobin was assessed by Haemoglobin analyzer and low serum levels haemoglobin (less than for M: 13 to 19 gm% and F: 12.0 to 15 gm %), Serum ferritin level determined by microparticle enzyme immunoassay (Normal range female: 18 – 115 ng/ml, Male: 30-300 ng/ml, Children: 7-140 ng/ml), Serum TSH level (0.4 to 4.0 milli-international units per litre). Collected parameters regarding clinical and laboratory data (serum vitamin B12, CBC, Ferritin, and TSH) of hyperpigmentation patients and normal control population.

Statistical Analysis: Statistical package for Graph pad prism software version (5.0) was used for data entry and analyzing, aided by Microsoft excel 365 for calculations, plotting graphs and tables. Descriptive data were presented for continuous variables as mean ± SD, while qualitative data description done by calculating number and percentage (n, %). T-test was used for statistical analysis was used for significant associations, P-value ≤ 0.05 considered statistically significant.

RESULTS:

Characteristics of the Population: A Total number of 70 HP patients, males 28 (40%) and females 42 (60%) and 22 controls (17 males and 5 females) were included in the study **Table 1.**

TABLE 1: SEX WISE DISTRIBUTION

Gender	Hyperpigmentation Patients (n= 70)	Percentage (%)
Male	28	40 %
Female	42	60 %
Total	70	100 %

There were a majority of patients belonged to the age group of 11 to 40 years **Table 2**. In HP patients, the mean age of 26.49 years and standard deviation of 10.08, and in the normal control group, the mean age of 35.45 years and standard deviation of 8.744. There was no statistical difference between the groups in terms of sex (P = 0.2554).

TABLE 2: AGE RANGE DISTRIBUTION OF PARTI-CIPANTS

Age Range (Yrs)	Frequency	Percentage (%)
0-10	00	00
11-20	28	40 %
21-30	20	28.57 %
31-40	17	24.28 %
41-50	04	5.71 %
>50	01	1.42 %
Total	70	100 %

Clinical Features: The common features were dark skin coloration on face, neck, elbow, knee, surround to eyes, on fingers, *etc*.

TABLE 3: HYPERPIGMENTATION PATIENTS SUB DIVIDES INTO DIFFERENT TYPES

Types	Number of Patients	Percentage (%)
Acanthosis nigricans	17	24.0%
Knuckle pigmentation	18	25.71%
Post inflammatory hyperpigmentation	07	10%
Generalized hyperpigmentation	04	5.71%
Peri-orbital hyperpigmentation	05	7.14%
Nail / oral pigmentation	01	1.40%
Peri-oral pigmentation	12	17.14%
Facial pigmentation	04	5.71%
Prurigo nodularis pigmentation	01	1.40%
Congenital erythroderma pigmentation	01	1.40%
Total	70	100 %

In this study Hyperpigmentation, patients can be divided based on the location of dark coloration on the body. In this study, a maximum number of cases, 18 (25.71%) cases are of knuckle pigmentation, 17 (24%) cases of acanthosis nigricans, 7 (10 %) cases of post-inflammatory hyperpigmentation, 4 (5.71%) cases of generalized hyperpigmentation, 5 (7.14%) cases of peri-orbital hyperpigmentation, 1 (1.40%) cases of nail and oral hyperpigmentation, 12 (17.14%) cases of peri-oral hyperpigmentation, 4 (5.71%) cases of facial hyperpigmentation, 1 (1.40%) case of Prurigo nodularis pigmentation and 1 (1.40%) case of Congenital erythroderma pigmentation **Table 3.**

FIG. 1: KNUCKLE PIGMENTATION

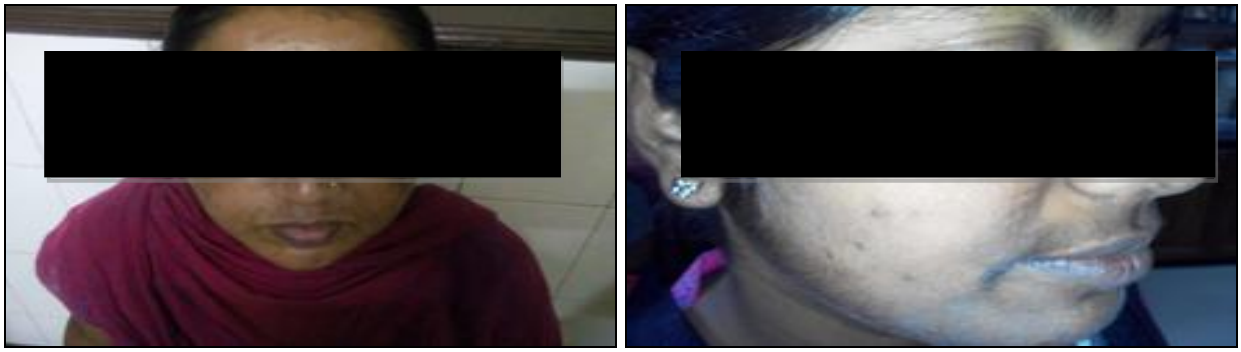

FIG. 2: FACIAL AND PERI ORAL PIGMENTATION

FIG. 3: POST-INFLAMMATORY HYPERPIGMENTATION

FIG. 4: ORAL HYPERPIGMENTATION

Laboratory Data:

Evaluation of CBC: The serum level of haemoglobin (13.58 ± 8.74 gm %) in hyperpigmentation patients was compared to normal control population (11.81± 2.41 gm %), which was statistically significant (P=0.0016**). Also, MCH (0.0082**) and MCHC (<0.001***). Even though hyperpigmentation was an important general examination finding, it did correlate with the duration of symptoms. Other CBC parameters did not show any significant difference between test population and control with the exception of PCV, MCV, and MCH **Table 4.** Out of 58 HP patients investigated for serum Haemoglobin, 5.17% patients showed Serum haemoglobin level less than 7 gm %, 18.96% showed haemoglobin level between 7 to 10 gm %, 46.55 % patients showed haemoglobin level between 10 to 13 gm %,

and 29.31% patients showed haemoglobin more than 13 gm %. The haemoglobin level in the HP group (11.81 ± 2.414 gm %) was found to be lower than the control group (13.58 ± 8.744 gm %) **Table 5**. This difference was statistically significant (P-value 0.0016 < 0.005).

TABLE 4: CBC PARAMETER OF HYPERPIGMENTATION PATIENTS AND NORMAL CONTROL

Parameters	Hyperpigmentation Patients (N=58) (Mean ± SD)	Control (N=22) (Mean ± SD)	P
Hemoglobin	11.81 ± 2.414	13.58 ±8.744	0.0016**
Total RBC	4.77 ± 0.881	4.744 ± 0.532	0.8671 ns
Total WBC	7704 ± 2332	7136 ± 1407	0.2885 ns
Total platelets	348569 ± 105653	274636 ± 55436	0.0026ns
Polymorphs	61.43 ± 8.842	63.545 ± 6.084	0.3058 ns
Lymphocytes	34.78 ± 8.645	32.818 ± 6.169	0.7416 ns
Eosinophils	2.293 ± 0.16	2.318 ± 0.476	0.8928 ns
Monocytes	1.579 ± 0.680	1.318 ± 0.476	0.1038 ns
PCV	37.12 ± 7.317	38.504 ± 2.853	0.3911ns
MCV	75.71 ± 14.91	82.059 ± 7.565	0.0613 ns
MCH	25.50 ± 5.965	29.177 ± 3.461	0.0082**
MCHC	31.72 ± 3.926	35.495 ± 1.142	<0.001***
RDW	41.66 ± 9.594	40.909 ± 3.375	0.7782 ns

TABLE 5: HEMOGLOBIN IN HYPERPIGMENTED PATIENTS COMPARE WITH CONTROL

Hemoglobin	Hyperpigmented Patients (N = 58)			Controlpopulation (N=22)			P
Range (gm %)	Number	%	Mean ± SD	Number	%	Mean ± SD	
<7	03	5.17	6.733 ± 0.251	0	0	---	0.0016**
7 – 10	11	18.96	8.927±0.972	0	0	---	
10 – 13	27	46.55	11.89 ± 0.775	7	31.81	12.0 ± 0.568	
>13	17	29.31	14.42 ± 1.222	15	68.18	14.31 ± 0.590	
Total	58	100	11.81 ± 2.414	22	100	13.58 ±8.744	

Evaluation Vitamin B12 Level: Out of Total 55 HP patients investigated for serum vitamin B12, 36.36 % patients showed vitamin B12 level less than 212 pg/ml, 20% patients showed B12 level between 212 to 300 pg/ml, 18.18% patients showed vitamin B12 between 301 to 400 pg/ml and 27.27% patients showed vitamin B12 more than 400 pg/ml.

The vitamin B12 level in the HP group (Mean ± SD, 293.4 ± 137.2) was found to be slightly higher than the control group (Mean ± SD, 189.5 ± 138.6) **Table 6**. Only 36% HP patients showed a deficiency of vitaminB12 (less than 211 pg/ml). As again, this 77% control population showed a deficiency of vitamin B12. Cetrarate to expectation, vitamin B12 level in HP group was found to be slightly higher than the control group. The observed data, therefore, did not support the hypothesis that deficiency in vitamin B12 can be one of the causes of HP.

TABLE 6: VITAMIN B12 COMPARE WITH HYPER-PIGMENTED PATIENTS

Vitamin B12	Number of Patients	Percentage
Normal	35	63.63%
Deficiency	20	36.36%
Total	55	100%

TABLE 7: VITAMIN B12 IN HYPERPIGMENTED PATIENTS COMPARE WITH NORMAL CONTROL

Vitamin B12 (pg/ml)	Hyperpigmentation (N=55)			CONTROL (N=22)			P
	Number	Percentage	Mean ±SD	Number	Percentage	Mean ± SD	
< 212	20	36.36	153.7 ± 34.87	17	77.27	137.2 ± 47.75	
212 – 300	11	20	278.6 ± 17.95	02	9.09	257.5 ± 58.69	
301- 400	10	18.18	341.5 ± 31.83	02	9.09	331.0 ± 12.73	0.0033**
>400	15	27.27	480.0 ± 95.56	01	4.54	661.0 ± 0.0	
Total	55	100	293.4 ± 137.2	22	100	189.5 ± 138.6	

Evaluation of Ferritin Level: Out of 55 HP patients investigated for serum ferritin, 44.89% showed ferritin level less than normal (<15 ng/ml), 26.53% patients showed ferritin level between 15-30 ng/ml, 26.53% patients showed ferritin level between 31-211 ng/ml and 2.04% patient showed ferritin level more than 211 ng/ml **Table 7**. The serum ferritin level in the HP group (Mean ± SD, 44.04 ± 101.7 ng/ml) was found to be slightly

higher than the control group (Mean ± SD, 89.22 ± 83.64 ng/ml). This difference was statistically significant (P-value 0.0072< 0.005).

TABLE 8: SERUM FERRITIN PATIENTS COMPARE WITH CONTROL

Ferritin (ng/ml)	Number Of Patients (N = 49)			Control (N = 22)			P
	Number	Percentage	Mean ± SD	Number	Percentage	Mean ± SD	
<15	22	44.89 %	7.867 ± 3.036	02	9.09%	10.65 ± 0.356	
15-30	13	26.53 %	21.80 ± 4.366	04	18.18%	23.78 ± 1.866	
30-211	13	26.53 %	78.26 ± 55.12	14	66.63%	89.96 ± 50.14	0.0727**
>212	01	2.04 %	684.0 ± 0.0	02	9.09%	293.1 ± 41.22	
TOTAL	49	100 %	44.04 ± 101.7	22	100%	89.22 ± 83.64	

Evaluation of TSH Level: Out of the 39 patients with hyperpigmentation, 2.56 % showed TSH level below normal (<3.0 miu/ml), 7.69% showed TSH level above Normal range (more than 5.0 miu/ml) and 89.74 % showed in the normal range (0.3 to 5.0 miu/ml). TSH level in HP group was found to be slightly higher than the control group. Which was statistically not significant (P > 0.005) **Table 9.**

TABLE 9: TSH LEVEL OF HYPERPIGMENTED PATIENTS AND NORMAL CONTROL

TSH (miu/ml)	Hyperpigmentation Patients (N = 39)			Normal Control (N = 22)			P
	Number	Percentage	Mean ± SD	Number	Percentage	Mean ± SD	
Less than 0.3	01	2.56 %		00	00	----	
0.3 to 5.0	35	89.74 %		22	100 %	1.541 ± 0.1702	0.0530^{ns}
More than 5.0	03	7.69 %		00	00	---	
Total	39	100 %	3.074 ± 3.115	22	100 %	1.541 ± 0.1702	

In this study, Laboratory data (Haemoglobin, Vitamin B12, Ferritin, and TSH) of hyper-pigmentation patients compared with normal control. Haemoglobin of hyperpigmented patients was (11.81 ± 2.414 gm %) compare with Normal control (13.58 ±8.744 gm %). P-value was 0.0016** and significant. Vitamin B12 of hyperpigmented patients was (293.4 ± 137.2 pg/ml) compare with Normal control (189.5 ± 138.6 pg/ml). P-value was 0.0033**and significant. Ferritin of hyperpigmented patients was (44.04 ± 101.7 ng/ml) compare with Normal control (89.22 ± 83.64 ng/ml). P-value was 0.0727** and significant. TSH of hyperpigmented patients was (3.074 ± 3.115 miu/ml) compare with Normal control (1.541 ± 0.1702 miu/ml). P-value was 0.0530 and non-significate **Table 10.**

TABLE 10: MEAN AND SEM OF HYPERPIGMENTED PATIENTS AND NORMAL CONTROL

Variables	Hyperpigmented Patients (Mean ± SD)	Normal Control (Mean ± SD)	P
Haemoglobin	11.81 ± 2.414	13.58 ±8.744	0.0016**
Vitamin B12	293.4 ± 137.2	189.5 ± 138.6	0.0033**
Ferritin	44.04 ± 101.7	89.22 ± 83.64	0.0727**
TSH	3.074 ± 3.115	1.541 ± 0.1702	0.0530^{ns}

DISCUSSION: Indian population shows great inconsistency in skin color [30]. Hyperpigmentation is present in a variety of tissues in the body; the initiation and extent of pigmentation can be influenced by several intrinsic and extrinsic factors [31]. Common factors for hyperpigmentation are nutritional and metabolic imbalances [32].

Vitamin B12, Haemoglobin, ferritin and TSH level in serum influence its effects on skin hyper-pigmentation. This study of HP was conducted in Aravalli district in Gujarat, India. We found that HP patients were more possibilities to due to nutritional deficiency. In our study we found haemoglobin and Ferritin responsible for hyperpigmentation but Vitamin B12 and TSH produce less significant effects on hyper-pigmentation. An important clinical presentation found in this study was hyperpigmentation of the extremities, particularly of the knuckles, found in 25.71%. This is a relatively consistent finding so that the index of suspicion rises significantly in those patients with knuckle hyperpigmentation. In Hyperpigmentation 36.36% of patients have very low serum vitamin B12 levels. Determining the cause of vitamin B12 deficiency was not possible

due to logistic constraints. In Hyperpigmentation 22.13% Patients have very low serum Haemoglobin levels, and 44.89% of patients have very low serum Ferritin levels. Further well Designed, larger epidemiologic studies are required to confirm the increased prevalence of vitamin B12, haemoglobin, and Ferritin deficiency in this region. TSH level was normal. Thus, it may be considered only as a pilot study as north Gujarat of India has a lack of literature regarding vitamin B12, Haemoglobin, and Ferritindeficiency and the importance of skin manifestations as a clinical pointer to symptomatic vitamin B12, Haemoglobin, and Ferritin deficiency. Thus, this study has demonstrated the occurrence of symptomatic vitamin B12, Hb, and ferritin deficiency in this north Gujarat of the country and has highlighted the importance of cutaneous manifestations as a clinical marker in such patients. However, large-scale population-based studies are required to validate our findings.

CONCLUSION: Hyperpigmentation is a common dermatological disorder. In our study, nutritional and metabolic factors responsible for hyper-pigmentation. We find out haemoglobin, vitamin B12, and Ferritin were important factors for HP. The occurrence of hyperpigmentation in patients with vitamin B12, Haemoglobin, and Ferritin level correlates with the duration of symptoms.

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