



ISSN NO. 2320-5407

Journal Homepage: [-www.journalijar.com](http://www.journalijar.com)

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI:10.21474/IJAR01/12899
DOI URL: <http://dx.doi.org/10.21474/IJAR01/12899>



INTERNATIONAL JOURNAL OF
ADVANCED RESEARCH (IJAR)
ISSN 2320-5407
Journal Homepage: <http://www.journalijar.com>
Journal DOI:10.21474/IJAR01

RESEARCH ARTICLE

THYROID DISORDERS IN PATIENTS WITH MELASMA

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Manuscript Info

Manuscript History

Received: 20 March 2021
Final Accepted: 24 April 2021
Published: May 2021

Key words:-

Hypothyroidism, Hyperthyroidism,
Melasma, Thyroid Disorders

Abstract

Background and objectives: Melasma, a common pigmentary disorder is major cosmetic concern among patients. The aim of our study was to determine the frequency of thyroid disorders in melasma cases.

Methodology: This observational study was conducted at RIHS Dermatology Department Islamabad from 20th Feb–20th May 2021. Diagnosed cases of melasma (>18 years) were selected via consecutive sampling technique. The medically/surgically treated cases of thyroid, melasma secondary to other dermatosis, organ failure, Addison's disease, pregnancy and subclinical thyroid disorders were excluded. After detailed clinical evaluation, thyroid status documented on the basis of thyroid function tests. Data analysed by SPSS with significant p-value < 0.05.

Results: Amongst 150 melasma cases; 117 (78%) females and 33 (22%) males, mean age was 35.45±9.68 years. 36 (24%) were euthyroid, 109 (72.7%) hypothyroid and 5 (3.3%) hyperthyroid. Mean TSH was 1.82±18.64 mIU/L. 75 (50%) had epidermal, 38 (25.3%) dermal and 37 (24.7%) mixed melasma, hypothyroidism frequent in all three types. Dermal melasma frequent in 41-50 years, epidermal in 20-30 years and mixed in 31-40 years. Thyroid status had significant association with age group, hypothyroidism more common in 41-50 years and Euthyroid in <30 years. Obesity observed in 55 (36.7%) having significant association with hypothyroidism. Mandibular melasma observed in 88%, malar 77.3%, centro-facial 18.7% and neck melasma 9.3%.

Conclusion: Thyroid disorders, particularly hypothyroidism is frequent among melasma cases. Authors recommend to screen all melasma cases regardless of age or gender for thyroid disorders, in particular obese cases. The diagnosis and management of thyroid disease in

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melasma cases may improve quality of life, prevent thyroid related complications and improve outcome of melasma treatment.

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Introduction:-

Melasma is an acquired, benign, localized, chronic, relapsing, treatable, challenging disorder of pigmentation which is characterized by bilateral blotchy or spotty brownish macules or patches with irregular linear or confluent borders involving all over body but most commonly involve face and less commonly neck and forearm. The extra-facial melasma is less common type, only seen in postmenopausal females and can involve neck and arms. The word melasma is from Greek word "melas" which means black, also known as cholasma while occurring in pregnancy, which is derived from "chloro" which means green colour.

Melasma is mostly commonly seen in young to middle aged Asian, Hispanics or African females who have dark skin colour of Fitzpatrick skin type III to V, less common in males. The prevalence is 8% -30% in the population of south East Asia. Multiple factors like pregnancy, oral contraceptive pills, exposure to sunlight, cosmetic products, emotional factor, pollution, phototoxicity, nutritional deficiency, hormonal imbalance, hepatic disease, genetic factors, thyroid dysfunction, ovarian tumours and anti-epileptic drugs can cause melasma.^[1,2,3,4,5,6,7]

Clinically, there are three types of melasma rash distribution pattern. Commonest sites are Centro-facial (65%), malar (20%), mandibular (15%). The Centro-facial pattern is most common pattern which involves sides of forehead, nose, cheeks, upper lip (except philtrum) and chin. In the malar and mandibular type, the lesions are more localized and only involve cheeks, nose and ramus of mandible. Malar pattern is more common in men while Centro facial is common pattern in females.

Wood's lamp illumination helps in determination the depth of melanin pigment and treatment outcome of melasma. On Wood's lamp illumination, melasma can be classified into four groups that are epidermal, dermal, mixed and indeterminate.

Abnormal thyroid function may be important cause of hyperpigmentation or rash of melasma which is treatable and hypothyroidism is found to be associated with melasma in many cases. Serum levels of TSH, anti TPO, anti microsomal antibodies and anti-thyroglobulin antibody are significantly higher in patients with melasma than those without melasma in certain studies.^[3,8,9,10,11] Abnormal levels of TSH were found in certain previous literature and it has significant strong relationship with the melasma. Subacute hypothyroidism may also lead to melasma secondary to autoimmune processes and this will cause the reason the age of onset and female predominance.

Also, there is a hypothesis that thyrotoxicosis may produce hyperpigmentation through an increased fragility of capillaries, deposition of hemosiderin and melanosis of basal layer.^[12] On the basis of histopathological evaluation, there is up-regulation of fibroblasts which may lead to increased growth of melanocytes, transfer of melanosomes and produces melanogenesis. The transcription study reveals the increase secretion of frizzled related protein 2 which induces melasma through microphthalmia associated transcription factor or tyrosinase upregulation via beta catenin signalling. There is a downregulation of H19 gene in lesional and perilesional skin of melasma which induces stimulation of melanogenesis and transfer of melanin to keratinocytes.

Kang et al found upregulation of many melanin biosynthesis related genes and melanocytes markers like TYR, MITF, SILV and TYRP1 in melasma skin. Biological pathways genes like Wnt pathway modulation, genes in prostaglandin synthesis and fatty acid metabolism are also affected in melasma. There is a decreased stimulation of Wnt inhibitory factor 1 (WIF-1) in the affected skin of melasma which leads to melanogenesis and transfer of melanosome.

Several literatures show association of thyroid dysfunction in patients with melasma, especially thyroid autoimmune disorder and hypothyroidism. The exact mechanism of production of pigmentation by thyroid dysfunction is not known. The hypothesis is that inflammatory cytokines induced by thyroid hormones, especially in hyperthyroidism so melasma can be triggered with any condition which produces inflammation. There is a high levels of circulatory pro inflammatory cytokines seen in the patient of hyperthyroidism with melasma.^[13,14,15,16,17,18]

Melanogenesis induces through stimulation of ACTH and MSH which can activate melanocortin receptors in melanocytes. Important cause in the pathogenesis of melasma is immunoreactivity against α -MSH and melanocortin system which interact with the hypothalamic-pituitary-thyroid axis.^[16] Melasma creates a physical and mental health issues in females due to emotionally, socially economically as a cost-effectiveness and severely effects on quality of life of patients because of cosmetic concern.^[8,9,10,11,12]

So far, limited number of regional studies are available regarding association of melasma with thyroid disorders. Hence, the aim of present study was to determine the thyroid disorders in patients with melasma. This will help us identify the cases of melasma to be screened for thyroid disorders on the basis of gender, age group and type of melasma. Also, this may help us develop a clinical approach to diagnose and manage thyroid disorders that is a systemic disease via dermatological manifestation.

Methodology:-

This observational study was conducted in Rawal institute of Health Sciences in the Department of Dermatology from 20th Feb to 20th May 2021 after approval by the institutional ethical committee. **Inclusion criteria:** Diagnosed case of melasma > 18 years of both genders presenting to Department of Dermatology were included in this study. **Exclusion criteria:** Patients who were unable to give informed consent, taking antithyroid drugs or have undergone thyroidectomy or radioactive iodine ablation, melasma due to other dermatosis, having any organ failure, Addison's disease or pregnancy, patients taken drugs with side effects of melasma (i.e., anticonvulsants, oral contraceptives, TTC), or drugs that cause deranged thyroid function tests (i.e., amiodarone, lithium, oestrogens, anti-epileptics, rifampicin). The cases of subclinical hypo or hyperthyroidism were also excluded.

Total 150 patients of both the genders and age > 18 years were included. Subjects were selected through consecutive sampling technique on the basis of characteristic features (clinical features) of melasma and informed consent was obtained. The detailed history, dermatological, systemic and thyroid examination was performed. Height and weight of the patients was documented and BMI calculated to label each case as obese or non-obese. The routine baseline investigations like Complete blood counts and specific tests like TSH, T3, T4 were advised and results entered into specifically designed proforma. Cases were labelled as hyperthyroid, hypothyroid or euthyroid on the basis of thyroid function tests.

The data was analysed by SPSS. The frequency and percentages were calculated for qualitative variables (i.e., gender, obesity, thyroid status, type of melasma and site of melasma). Mean and standard deviation calculated for age. The chi-square test was applied to study association of thyroid status with various variables (i.e., gender, age, type of melasma, obesity, marital status, type and site of melasma). The p-value < 0.05 was considered statistically significant. Data presented as tables, pie chart and bar graph.

Results:-

Amongst 150 cases of melasma, there were 117(78%) females and 33(22%) males. Mean age was 35.45±9.68 (range 20-50) years. 77(51%) patients were married and 73(48.3%) were unmarried. Obesity (BMI>30) was observed in 55(36.7%) cases. Based on the thyroid function tests 36(24%) patients were euthyroid and 114(76%) patients had thyroid disorder; i.e., 109(72.7%) were hypothyroid and 05(3.3%) cases were hyperthyroid. The mean thyroid stimulating hormone (TSH) level observed was 1.82±18.64 with a range of 0.003-100 mIU/L. The mean value of TSH had significant association with the various types of melasma (**p<0.0001; table 3**).

Based on the findings of woods lamp examination, 75(50%) had epidermal and 38(25.3%) patients had dermal melasma, 37(24.7%) had mixed melasma (**fig 1**). There was significant association of type of melasma with thyroid status (**p=0.006, table 1**). All the three types being more common in hypothyroid cases as compared to euthyroid and hyperthyroid cases. Also, there was significant association of type of melasma with age groups (**p=0.021, table 2**). The Dermal melasma being more common in 41-50 years age group, epidermal melasma in 20-30 years age group and mixed melasma in 31-40 years age group.

Thyroid status also found to have significant association with age group in melasma cases (**p=0.018, table 2**). Hypothyroidism was more common in 41-50 years age group however it was frequently observed in less than 40 years patients also. Euthyroid state was frequent in less than 30 years age group. Thyroid status had significant association with obesity based on BMI as well 48(87%) of the obese cases were hypothyroid (**p=0.009, table 1**).

The distribution of melasma on various body parts showed that mandibular melasma was most frequent i.e., 132(88%) cases, followed by malar type in 116(77.3%), Centro-facial 28(18.7%) and neck melasma 14(9.3%) cases (table 1, fig 2).

Variables	Amongst all n=150	Hypothyroid n=109	Euthyroid n=36	Hyperthyroid n=05	P-value
Age (mean+SD) Range (years)	35.45+9.68 (20-50)	37.08+9.51 (20-50)	30.39+8.85 (20-48)	36.40+7.89 (30-45)	0.001
Gender					
• Males	33(22%)	21(63.6%)	12(36.4%)	0(0%)	0.101
• Females	117(78%)	88(75.2%)	21(20.5%)	05(4.3%)	
Marital status					
• Married	77(51.3%)	63(81.8%)	12(15.6%)	02(2.6%)	0.034
• Unmarried	73(48.7%)	46(63%)	24(32.9%)	03(4.1%)	
Obesity					
• Non-obese	95(63.3%)	61(64.2%)	30(31.6%)	04(4.2%)	0.009
• Obese	55(36.7%)	48(87.3%)	06(10.9%)	01(1.8%)	
Type of Melasma (on woods lamp)					
• Epidermal	75(50%)	47(62.7%)	27(36%)	01(1.3%)	0.006
• Dermal	38(25.3%)	31(81.6%)	4(10.5%)	03(7.9%)	
• Mixed	37(24.7%)	31(83.8%)	05(13.5%)	01(2.7%)	
Site of Melasma					
• Malar	116(77.3%)	81(69.8%)	30(25.9%)	05(4.3%)	0.250
• Mandibular	132(88%)	99(75%)	28(21.2%)	05(3.8%)	0.079
• Forearm	02(1.3%)	02(1.8%)	0(0%)	0(0%)	0.683
• Centro-facial	28(18.7%)	24(85.7%)	04(14.3%)	0(0%)	0.191
• Extra-facial	06(4%)	06(100%)	0(0%)	0(0%)	0.309
• Neck	14(9.3%)	08(57.1%)	04(28.6%)	02(14.3%)	0.045
• Other sites	06(04%)	04(66.7%)	02(33.3%)	0(0%)	0.792

(Test of significance Chi-square test; significant $p < 0.05$)

Table 1:- Representing the demographic variables, obesity, site and type of melasma in relation to the thyroid status of melasma cases (n=150).

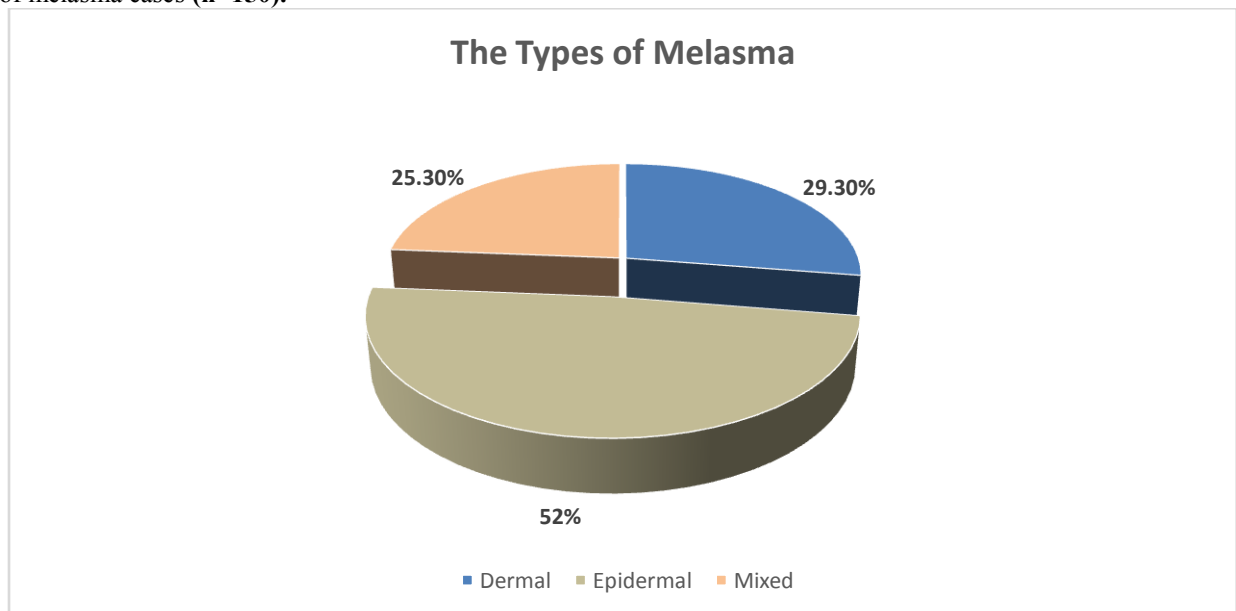


Fig 1:- The pie chart representation of the types of melasma with respect to involvement of skin layers and depth (n=150).

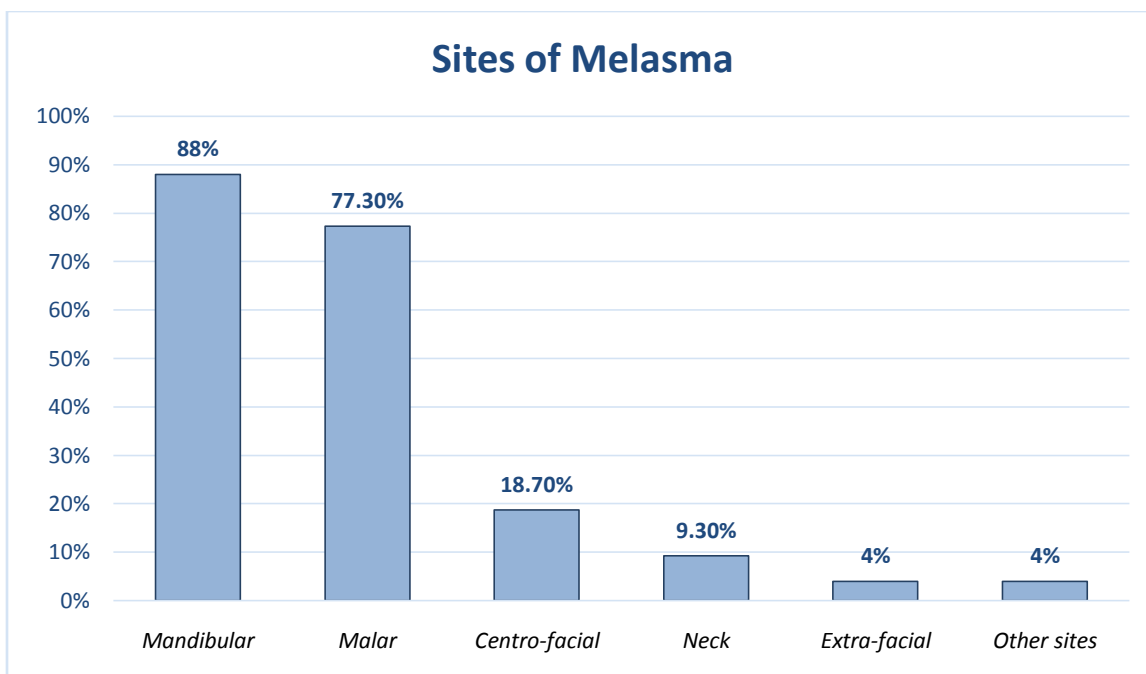


Fig 2:- The bar graph representation of the sites of involvement of melasma(n=150).

Variables	Amongst all n=105	20-30 years n=59	31-40 years n=39	41-50 years n=52	P-value
Melasma Type					0.021
• Epidermal	75(50%)	35(46.7%)	20(26.7%)	20(26.7%)	
• Dermal	38(25.3%)	31(81.6%)	4(10.5%)	03(7.9%)	
• Mixed	37(24.7%)	11(29.7%)	14(37.8%)	12(32.4%)	
Thyroid status					0.018
• Hypothyroid	109(72.7%)	35(32.1%)	32(29.4%)	42(38.5%)	
• Euthyroid	36(24%)	22(61.1%)	07(19.4%)	07(19.4%)	
• Hyperthyroid	05(3.3%)	02(40%)	0(0%)	03(60%)	

(Test of significance Chi-square test; significant $p < 0.05$)

Table 2:-The types of melasma (on the basis of woods lamp examination) and Thyroid status of melasma cases in relation to various age groups (n=150).

(Test of significance Chi-square test; significant $p < 0.05$)

Thyroid stimulating hormone (n=150)	Epidermal (n=75)	Dermal (n=38)	Mixed (n=37)	p-value
TSH levels (mean+SD) mIU/L 1.82+18.64 (0.003-100)	1.16+12.68 (0.01-60)	2.85+26.26 (0.003-100)	2.07+13.82 (0.005-60)	<0.0001

Table 3:- Presenting the mean thyroid stimulating hormone levels in relation to various types of melasma (n=150).

Discussion:-

Hyperpigmentation has been observed to be associated with many endocrine disorders, such as hemochromatosis and Addison's disease while hyperpigmentation due to thyroid dysfunction is rarely established in the previous studies. The smooth functioning of skin depends on circulation of normal thyroid hormones. Thyroid gland dysfunction presents with various clinical features. The thyroid gland dysfunction is one of the second most common endocrine problem which may be associated with variety of skin manifestations such as melasma.^[3,14]

In our study there were one hundred and fifty of melasma amongst which more than 3/4th were females and less than 1/4th were males. The ratio of female: males is 3.5:1 in our study which is lower than studies done by Shamma et

I,SumanBabu and HinaMehmood,Satin,SimplepreetKaur et al which showed 7.6:1, 7.1:1,5:1,4.2:1,10:1 respectively.^[1,2,3,18,19] Higher female preponderance in our study may be due to autoimmunity against thyroid gland which leads to thyroid dysfunction,e.g.,hypothyroidism or hyperthyroidism.^[1,14,20] According to literature, melasma most commonly seen in females during child bearing age in 2nd or 3rd decades which supports hormonal relationship in the aetiology.^[16] Subacute hypothyroidism may also lead to melasma secondary to autoimmune processes and this be the reason for younger age of onset and female predominance.^[1] However, in this study we excluded the subclinical and sick thyroid cases.

Mean age of patients in our study was thirty-five years with range of twenty to fifty yearswhile AsmaJaved,SimplepreetKaur,HinaMehmood and Suman Babuwas found 30 to 34 yearsmean ages respectively^[2,3,19,20] which coincides with our study.However, Shamma aboobaker and Satin showed higher mean of age that are 40.2±9 and 40.8 years respectively.^[1,18]

In our study out of 150 patients,1/4th of the cases waseuthyroid and 3/4th had thyroid dysfunction,i.e., 72.7%were hypothyroid and 3.3%cases were hyperthyroid as compared to much less incidence of thyroid disorders (53.65%) in study by Yeaser et al^[21] while Alka Dogra et al showed 23.7 % of melasma in thyroid disease.^[24]

The exact mechanism of production of pigmentation by thyroid dysfunction is not known. One of the hypotheses is that inflammatory cytokines induced by thyroid hormones may be responsible for hyperpigmentation, especially in hyperthyroidism. Hence,melasma can be triggered by any condition which produces inflammation.There is a high level of circulatory pro-inflammatory cytokines seen in the patients of hyperthyroidism with melasma.Melanogenesis occurs in response to inflammatory stimuli which respond by epidermal melanin unit.^[13,14,15,16,17,18]

Hypothyroidism is found to be associated with melasma in many cases. Serum levels of TSH, anti-TPO antibodies, anti-microsomal antibodies and anti-thyroglobulin antibody are significantly higher in patients with melasma than those without melasma in certain studies.^[3,8,9,10,11] Abnormal levels of TSH was found in certain previous studies and it has significant strong relationship with the melisma and its severity .

Shamma aboobaker,Kiani,Almani, RezvanTalaee et al,Simplepreet,Suman Babu showed 24%,37.8% and 31.5%,10% and 5 cases of hypothyroidism in their studies respectively.^[1,3,19,22] which showed lesser thyroid involvement in melasma patients than our study.^[1] While no case of hyperthyroidism was reported by study of Suman babu but we found few cases.^[2,19] Similarly,HinaMehmoodet al showed 19.5% cases of thyroid dysfunction, 17.3% cases of hypothyroidism and only 3 cases of hyperthyroidism in their study^[3] while thyroid dysfunction was observed by Mogaddam et al in 18.5%, hypothyroidism in 17.1% ad hyperthyroidism in 1.4% in Iranian study^[3,25] but our study showed higher percentage of thyroid dysfunction(both hypothyroidism and hyperthyroidism) in patients with melasma than other studies.As per literature,risk of thyroid dysfunction is 4 times higher in patients with melasma.^[19]

There was abnormal level of TSH(range from0.003mIU/L -100mIU/L)in our study and high TSH(i.e., hypothyroidism) in 105 patients and low TSH(i.e., hyperthyroidism) in 5 patients while Yeaser and Shamma aboobaker also found higher levels of TSH in their patients but lower range of upper limit of observed TSH than our study. High levels of TSH may be because of autoantibodies against the thyroid gland.^[1,21]

Lutfiet al found four times higher TSH in melasma patients than control group,e.g., 39.4% in their patients and they suggested that female hormones(oestrogen and progesterone)could trigger the melasma in patients with autoimmunity against thyroid gland^[19] Kiani et al noticed a relationship between melasma and hypothyroidism and thyroid autoimmunity.^[16]

RezvanTalaee and Niepomniszeze et al found statistical relationship between TSH and type of melasma (mild to severe), ($p=0.037$ & $p= 0.002$)^[21,22] while Sheth VM and Pandya didn't find any correlation between thyroid dysfunction and melasma.^[17] While Suman babu and Asma found levels of TSH (range from 2.01-3.01)that weren't very high in their patients withmelasma associated with hypothyroidism, this also doesn't coincide with our results.^[2,9] Tamega et al found high levels of TSH in 25.3% of patients with melasma and reportedmelasmain association of intense sunexposure with high levels of TSH.^[17] RezvanTalaee found severity of melasma with high TSH and there was a significant statically relationship between TSH and melisma^[21]

In our study, mandibular melasma was most frequent i.e., 88% followed by 77.3% malar and 18.7% Centro facial. While Centro facial is the most common type of melasma in literature all over the world but Simplepreet Kaur, Raseena Moosa found malar type of melasma in their studies^[19, 11] while Seray et al^[13] found Centro facial in 42.2% and malar 42.2% in their studies which doesn't coincide with our study.^[17] Mandypagar found only one case reported of mandibular type of melasma.^[23]

On wood's lamp examination of pigmented lesions, the pigment can be assessed and classified according to level of pigment. Our patients on wood's lamp examination had epidermal melasma most common type i.e., 50%, dermal 25% and mixed type of melasma 25%. While Shamma Aboobaker showed dermal melasma in 80%, epidermal in 20% and mixed in 20%.^[11] Simplepreet found 23% dermal, 58% epidermal and 19% mixed.^[19] Achar et al found dermal 54% i.e., the most common type, 21% epidermal and 24% mixed types respectively which are lower percentages of types of melasma and doesn't coincide with our study results.^[1, 8, 10, 1] By assessing the level of pigment, one can decide the prognosis of melasma, e.g., prognosis is good in epidermal melasma while poor in dermal melasma and needs long term treatment.^[1, 17]

There are limited regional studies addressing melasma with thyroid dysfunctions. This study provides us association of melasma with thyroid disorders in our population. There are certain limitations in our study like sample size and shorter duration of study and inability to obtain autoimmune thyroid profile due to financial constraints. Authors recommend further regional studies with better sample size, extended study duration and autoimmune thyroid profile workup in future studies. The results of this study will help us regarding earlier diagnosis of thyroid disorders associated with melasma, hence diagnosing and managing a thyroid disease i.e., a systemic disorder in patients presenting with dermatological complaint. This can help preventing long term complications and improving quality of life in our patients.

Conclusion:-

Thyroid disorders are frequent among melasma cases i.e., 76% of melasma cases. Mandibular and malar distribution of melasma were frequent. Hypothyroidism was the most common thyroid disorder with fewer hyperthyroid cases. Hence, it is recommended to screen all melasma cases regardless of age or gender for thyroid disorders, in particular patients with obesity. This may lead to identification of hypothyroidism a systemic endocrine disorder in dermatologically presenting melasma cases. We may conclude that the diagnosis and management of thyroid disease in melasma cases may improve quality of life, prevent thyroid related complications and improve outcome of melasma treatment as well.

Acknowledgement:-

We are thankful to all participants who were involved in this study and those who have helped either directly or indirectly.

Grant Support & Financial Disclosure:

None.

Conflicts Of Interest:

There was no conflict of interest of any authors.

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