

# Frequency of Hypothyroidism in Patients with Melasma in a Tertiary Care Hospital

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## ABSTRACT

**Objective:** To determine the frequency of hypothyroidism in patients with melasma presenting at a tertiary care hospital.

**Study Design:** Cross-Sectional Study.

**Place and Duration of Study:** This study was conducted at the Department of Dermatology, PNS Shifa Hospital, Karachi from 12<sup>th</sup> September 2020 to 11<sup>th</sup> March 2021.

**Materials and Methods:** After approval from the Hospital Ethical Review Committee, 145 patients reporting to Dermatology Department, PNS Shifa Hospital Karachi, clinically diagnosed as melasma and fulfilling the inclusion criteria, were enrolled. Informed consent was taken and all the patients were tested to see any thyroid hormone abnormality. A 2 ml venous blood sample was taken in a sterilized 5ml disposable syringe for each patient and sent to laboratory to check serum TSH and free T4.

**Results:** There were 40 (27.6%) males and 105 (72.4%) were females with mean age was 34.5±7.7 years. Hypothyroidism was found to be present in 31 (21.4%) patients. Out of these 31 hypothyroid patients, 22(71%) were young, females 19 (61%), obese 20 (65%), hypertensive 23 (74%), non-smokers 25 (81%), urban 18 (58%) and 25(81%) had no family history of melasma. Uncontrolled diabetes mellitus was seen in 60 (41.4%). Vitamin-D deficiency was found in 54 (37.2%) patients.

**Conclusion:** Hypothyroidism is seen in considerable number of patients presenting with melasma. These patients are usually young females, mainly from urban background with no family history and have tendency to be obese and hypertensive.

**Key Words:** Hypothyroidism, Melasma, MASI, Thyroid Function Tests, Diagnosis

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## INTRODUCTION

Melasma is an acquired pigmented disorder described as symmetrical blotchy or splotchy hyperpigmented macules and patches mainly localized in the sun-exposed body areas, namely chin, cheek, forehead, upper lip and rarely forearms.<sup>1</sup> Melasma is a common skin problem worldwide with a high burden among patients referred to dermatologists. Its prevalence varies from 8.8% in America to 40% in Asia being most common in India, Pakistan and Middle East. Pregnant ladies and those who use oral contraceptives (OCP) are particularly susceptible to develop melasma.

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The precise cause is unknown, however, a number of factors are implicated in the aetiopathogenesis of melasma. These include genetic influences, exposure to ultraviolet (UV) radiation, pregnancy, oestrogen-progesterone therapies, thyroid dysfunction, cosmetics and phototoxic and anti-seizure drugs.<sup>2</sup> The primary cells involved are the pigment producing melanocytes that originate from the neural crest and can be influenced by cells in close proximity (keratinocytes, fibroblasts).<sup>1,3</sup> Melasma primarily affects the visible parts of body most commonly face and causes remarkable emotional and social morbidity in both females and males.<sup>2,4</sup>

Melasma like hyperpigmentation occurs in a number of endocrine diseases, However, the occurrence of hyperpigmentation in thyroid dysfunctions is not often reported in the literature.<sup>3</sup> Hypothyroidism affects approximately 5% of the general population and 99% of affected patients suffer from primary hypothyroidism.<sup>5</sup> Hypothyroidism is generally under-recognized as many patients remain undiagnosed.<sup>6</sup> Common causes of hypothyroidism include iodine deficiency and autoimmune thyroiditis. It is diagnosed biochemically with serum thyroid-stimulating hormone (TSH)

concentrations above and thyroxine (T3 and T4) below the normal reference range.<sup>5</sup> Hypothyroidism is known to cause myriad of changes in the skin including thin, coarse and scaly skin (epidermal changes), myxedema, oedema of hands, feet and eyelids, pallor, carotenemia, (dermal changes), alopecia, dry and coarse hair, loss of lateral third of eyebrows, thin, brittle and dull nails (hair and nail changes), widespread xerosis especially on the extensor surfaces and hypohidrosis (sweat gland changes). Cold intolerance, purpura, dropping of upper eyelids and nerve entrapment syndromes are some other manifestations that can occur in hypothyroidism.<sup>7</sup> A number of thyroid hormone responsive genes including the keratin genes and the "hairless" (hr) genes have been identified which may be responsible for cutaneous changes produced under influence of thyroid hormones.<sup>7</sup> In literature, thyroid disorders are also described in association with several pigmentary disorders like vitiligo and post inflammatory hypopigmentation or hyperpigmentation.<sup>8</sup> There have been few studies highlighting the association of hypothyroidism and melasma. Higher levels of TSH have been reported in patients of melasma and thyroid hormones are considered to play an important role in melasma. The prevalence of hypothyroidism in melasma has variably been reported from 11% to 58% in these studies.<sup>9</sup>

The mechanism how thyroid hormones may affect melasma is not clear. Adrenocorticotropic hormone (ACTH) and Melanocyte stimulating hormone (MSH) probably activate melanocortin receptors in melanocytes, that induces melanogenesis. Increased sensitivity of melanocyte to MSH in patients of melasma can be suggested as one of the important factors in the pathogenesis of the disease. Moreover, interaction of melanocortin system with the hypothalamic-pituitary-thyroid axis is also established.<sup>11</sup> Higher circulating levels of pro-inflammatory cytokines seen in patients with thyroid disease also suggests that thyroid hormones induce production of inflammatory cytokines and epidermal-melanin unit in facial skin of melasma patients. Inflammatory stimuli cause pigmentation through melanogenesis. It can be postulated that melasma can be triggered by procedures that induce skin inflammation.<sup>10,11</sup>

Multiple treatment options are available for melasma like hydroquinone, Kligman's regimen, alpha and beta hydroxy acids, vitamin C, alpha arbutin, photoprotection, chemical and physical peeling and q-switch Nd-YAG laser but there is no effective and long lasting treatment because most of the available therapies aim at controlling melanogenesis and are not directed at the actual cause of increased pigmentation.<sup>12</sup> As face is the most affected area in melasma and there is no permanent treatment, patients suffer considerable

psycho-social distress.<sup>4</sup> If cause of the disease is established, it can be treated effectively by addressing the causative factors and patients can be saved from significant agony. Though thyroid hormones and thyroid autoimmunity is thought to play a role in the pathogenesis of melasma but the number of studies on this subject is few and the results are also conflicting.<sup>9-11</sup> This study was conducted to explore the possible association of hypothyroidism in patients with melasma and to generate local data by observing the magnitude of this association so that treatment can be rationalized on the basis of aetiology and patients managed in a better way.

## MATERIALS AND METHODS

It was a cross sectional study carried out in dermatology department, PNS Shifa Hospital Karachi from 12<sup>th</sup> September 2020 to 11<sup>th</sup> March 2021 after approval from hospital ethical review committee (ERC/2020/Der/08). Patients were enrolled through non probability consecutive sampling technique. Sample size was calculated according to WHO calculator which came out to be 145 using prevalence (p) of hypothyroidism in melasma as 24.3%<sup>9</sup> and margin of error (d) 5%. Patients of either gender and in the age range of 20-60 years, having darkening of localized facial skin for  $\geq 1$  month duration and clinically diagnosed as melasma by a consultant dermatologist, were included in the study. The pregnant, lactating ladies and the patients already on thyroid hormone replacement therapy, OCP, tetracyclines, quinolones, lithium, interferon and amiodarone were not included. The patients with autoimmune connective tissue disorders, hepatic insufficiency, chronic renal failure and hematological malignancies were also excluded. Informed consent was taken after explaining the procedure, risks and benefits.

The data was collected on a pre-designed proforma that included age, gender, residence (urban or rural), family history of thyroid disease, educational status, duration of diseases, site and extent of melasma and presence or absence of any other possible effect modifiers like hypertension, smoking, uncontrolled diabetes mellitus and vitamin D deficiency. All the recruited patients were tested to see any thyroid hormone abnormality. A 2 ml venous blood sample was taken in a sterilized 5ml disposable syringe and sent to laboratory to check for thyroid hormone status. The hypothyroidism was labeled when serum TSH  $\geq 10$  mU/L and serum free T4  $< 0.7$  ng/dl. The collected data was recorded and analysis was done by using SPSS-25. The stratification was done for age, gender, duration of diseases and post stratification Chi-square test was applied at 95% confidence interval and the p-value  $\leq 0.05$  was considered as statistically significant.

## RESULTS

There were 40 (27.6%) males and 105 (72.4%) were females. Mean age was  $34.5 \pm 7.7$  years with C.I (33.23-35.76), duration of disease was  $16.3 \pm 4.2$  months with C.I (15.6-16.98). 79 (54.5%) patients were resident of urban areas while 66 (45.5%) were resident of rural areas. Positive family history of thyroid disease was found to be in 34 (23.4%) patients. Educational status showed 14 (9.6%) illiterate, 26 (17.9%) primary education, 32 (22.1%) middle education, 14 (9.7%) secondary education while 59 (40.7%) had higher education.

**Table No.1: Stratification of confounders with respect to hypothyroidism**

Confounders	Hypothyroidism		P value
	Yes	No	
<b>Age (years)</b>			
20-40	22 (15.2%)	78 (53.8%)	0.786
>40	9 (6.2%)	36 (24.8%)	
<b>Gender</b>			
Male	12 (8.3%)	28 (19.3%)	0.118
Female	19 (13.1%)	86 (59.3%)	
<b>Duration (months)</b>			
1-12	17 (11.7%)	45 (31.0%)	0.125
>12	14 (9.7%)	69 (47.6%)	
<b>Hypertension</b>			
Hypertensive	23 (15.9%)	54 (37.2%)	0.008
Non-hypertensive	8 (5.5%)	60 (41.4%)	
<b>Smoking status</b>			
Smoker	6 (4.1%)	27 (18.6%)	0.610
Non-Smoker	25 (17.2%)	87 (60.0%)	
<b>Obesity</b>			
Obese	20 (13.8%)	60 (41.4%)	0.238
Non-Obese	11 (7.6%)	54 (37.2%)	
<b>Uncontrolled DM</b>			
Diabetic	15 (10.3%)	45 (31.0%)	0.327
Non-Diabetic	16 (11.0%)	69 (47.6%)	
<b>Residential status</b>			
Urban	18 (12.4%)	61 (42.1%)	0.625
Rural	13 (9.0%)	53 (36.6%)	
<b>Vitamin D deficiency</b>			
Yes	10 (6.9%)	44 (30.3%)	0.517
No	21 (14.5%)	70 (48.3%)	
<b>Family history</b>			
Positive	7 (4.8%)	25 (17.2%)	0.938
Negative	24 (16.6%)	89 (61.4%)	
<b>Educational status</b>			
Illiterate	3 (2.1%)	11 (7.6%)	0.9
Primary	6 (4.1%)	20 (13.8%)	
Middle	6 (4.1%)	26 (17.9%)	
Secondary	4 (2.8%)	10 (6.9%)	

Mean TSH was  $4.72 \pm 2.05$  with C.I (4.38-5.05) mU/L and free T4 was  $1.09 \pm 0.23$  with C.I (1.05-1.12) ng/dL. Uncontrolled diabetes mellitus was documented in 60 (41.4%), Vitamin-D deficiency in 54 (37.2%) hypertension in 77 (53.1%). 80 (55.2%) patients were obese while 33 (22.8%) were smoker. Hypothyroidism

was found to be in 31 (21.4%) patients. Stratification of age group, gender, duration of diseases, hypertension, smoking, obesity, un-controlled diabetes mellitus, residence (urban and rural), vitamin D deficiency, family history of thyroid disease and educational status was done with respect to hypothyroidism in order to assess significant difference as shown in Table 1.

## DISCUSSION

The precise aetiology of melasma has not been determined. However, multiple factors and associations have been implicated in its etiopathogenesis, including pregnancy, combined OCP, genetics factors, sun exposure, use of cosmetic products, certain drugs and thyroid dysfunction.<sup>2,4</sup> In our study we determined the frequency of hypothyroidism in melasma.

We found melasma more in females (>70%), as already established and may be attributed to peculiar hormonal environment (estrogens/oral contraceptive pills/pregnancy) in females.<sup>13</sup> Although men share the same clinico-histologic characteristics as in women, hormonal factors do not seem to play major significant role in men.<sup>13,14</sup>

Mean age, duration of melasma and geographical distribution (urban vs rural) seen in our patients was in agreement with previous studies.<sup>14,15</sup>

We observed melasma in all subgroups based on education status but majority (>40%) belonged to higher than secondary education group. This suggests the possible role of stress and emotions related to higher education, stressful working environment and high intellect in this subgroup which may be responsible for increased concern and psychosocial stigmatization related to the disorder.

Thyroid disorders are usually described in association with certain skin disorders like vitiligo, Sjogren syndrome, pretibial myxedema. Melasma is a common skin problem worldwide with a high burden among patients referring to dermatologists but no consistent scientific evidence exists regarding its association with thyroid disorders.<sup>16</sup> Cakmak et al.<sup>11</sup> showed higher TSH levels among patients with melasma as compared to those without, while in another study Talaei et al.<sup>18</sup> reported similar levels among subjects with and without melasma. However by combining the results of multiple studies, an association between hypothyroidism and melasma especially among women has been suggested<sup>16</sup> which is in accordance with the results of our study.

In our study, we observed hypothyroidism in 31 (21.4%) patients with mean level of TSH  $4.72 \pm 2.05$  mIU/ which is similar to previously reported but we had quite a higher mean level of free T4.<sup>11,17-19</sup> While doing stratification of confounders with respect to hypothyroidism, we could see that majority of the melasma patients were young, obese, non-smokers females from urban background with no family history

of hypothyroidism but statistically significant difference was noted in case of hypertension only. The difference in diabetes mellitus, residential status, vitamin D deficiency levels, and educational status were not statistically significant (Table1). Association of hypertension with hypothyroidism has also been reported earlier in the literature<sup>20</sup> and has to be further explored in larger studies.

We found hypothyroidism in patients of melasma in our study but we did not correlate the effect of thyroid hormone levels on severity of melasma. However, Rahman et al<sup>21</sup> did not observe any significant difference in thyroid hormone levels in patients with varying severity of melasma in their recent cross-sectional study on effect of free T4 and TSH on severity of melasma. Similar results were found when Syarif et al<sup>22</sup> studied the T3 and TSH in melasma severity in Padang, Indonesia.

There were certain other limitations in our study including small sample size, single centered study and regional variability. Moreover our study didn't clearly distinguish between primary or idiopathic and secondary melasma and because of cross sectional design, no risk factors and cause-effect relationship could be established. Therefore, further prospective large cohort studies are mandatory to evaluate trigger factors traditionally associated with melasma, as well as to verify the temporal association occurring between hypothyroidism and melasma.

## CONCLUSION

Hypothyroidism is frequently seen in association with melasma and these patients are usually young females from urban background with no family history and have tendency to be obese and hypertensive. Timely diagnosis and appropriate management of hypothyroidism may prevent this disease and save the patients from significant psychosocial distress.

### Author's Contribution:

Concept & Design of Study: Kiran Naz Khan  
 Drafting: Najia Ahmed, Khawaja Muhammad Salik  
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**Conflict of Interest:** The study has no conflict of interest to declare by any author.

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