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Melasma and Thyroid Autoimmunity: A Case Control Study to Evaluate Association, If Any

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ABSTRACT
Melasma is an acquired pigmentary disorder caused by increased melaocytosis and melanogenesis and found to be associated with thyroid autoimmunity. To ascertain if a relationship exists between serum levels of T3, T4, thyroid stimulating hormone (TSH) and anti-thyroid peroxides antibodies (anti-TPO) with melasma. This case-control study was carried out on 50 melasma cases and 50 age matched healthy females with no history of melasma as controls, their blood was drawn and examined for thyroid function tests including T3, T4, TSH and anti TPO antibodies. There was significant difference in the mean level of T3, T4, TSH and anti TPO between patient and control group. Serum T3 levels surpassed the normal levels in 75.8% of the patients and 49.1% of the controls, mean serum TSH levels was found to be 3.16 amongst melasma patients. In 24.7% of the patients and 6.8% of the controls, serum anti-TPO level was higher than normal. Thyroid disorders are frequent amongst melasma cases, the most common being hypothyroidism. Diagnosis and management of thyroid disease in melasma cases may improve quality of life, prevent thyroid related complications and improve outcome of melasma treatment.

INTRODUCTION

Melasma is a persistent, acquired disorder of hyperpigmentation of skin[1]. It is an innocuous affliction of human melanogenesis, typically presents as symmetrical, blotchy, brownish pigmentation with an erratic margin on the face and is a cosmetic concern[2,3]. The word melasma is derived from the Greek word "melas" meaning black, alluding to it's clinical presentation as brown macules. It is otherwise called as "chloasma" which takes its origin from the Latin word "chlóos" and the Greek word "cloazein" meaning greenish. Melasma is habitually seen in women of Asian, Hispanic and African ethnicity. It is more common in women than men with young-middle aged women being most affected[2]. It has a prevalence spanning from 9% in Hispanic populations in southern United States to 40% in Southeast Asians. It is rampant in Indian women. It is most discernible in premenopausal women, albeit men and postmenopausal women may be affected[4]. Elements kinding melasma include pregnancy, oral contraceptive pills, exposure to sunlight, phototoxicity, pollution, cosmetics, psychological factors, nutritional shortfalls, hormonal polarity, hepatic malady, heritable influences, affliction of the thyroid gland, ovarian tumours and anti-epileptic drugs like phenytoin[2,5,6]. A great many studies appraising the hormonal lineament in patients suffering from melasma have cognized significantly escalated levels of luteinizing hormone and lessened levels of serum estradiol theorizing ovarian debilitation of a mild degree having a role in the pathogenesis of melasma. Melanocompetent skin when exposed to visible light and long-wavelenght ultraviolet light A (UVA) consequently has demonstrated an upsurge in pigmentation eminently in patients with darker skin types (Fitzpatrick skin type IV-VI). Moreover, visible light induced pigmentation was found to be more intensive, stable and immutable compared with pigmentation brought about by UVA. This reiterates the exigency of employing physical sunscreen in the impediment of relapses of melasma[7]. Multitudinous studies inquesting melasma have authenticated that two factors culpable for inciting melasma are melanocytosis (expanded number of melanocytes) and augmented melanogenesis. Kim et al carried out a study which revealed heightened vascular endothelial growth factor (VEGF) in lesional skin of patients suffering from melasma[8]. The diagnosis of melasma is conventionally clinical[9]. Futhermore, treating the vascular component along with the pigmentation provides better results and reduces chances of further relapse of melasma[10]. A transcriptional analysis in melasma skin samples implemented by Kang et al divulged the findings of 279 genes being upregulated and 152 were found to be downregulated. A myriad of genes involved in melanin biosynthesis in addition to melanocyte markers for instance tyrosinase (TYR), Microphthalmia-associated transcription factor (MITF), silver locus protein homolog (SILV) and Tyrosinase related protein 1(TYRP1) were found to be upregulated in melasma skin[11]. Several other genes involved in other biological pathways were found to be affected. These include Wnt pathway modulation genes, genes involved in prostaglandin synthesis and fatty acid metabolism. Chronic UV exposure causes disturbed lipid metabolism, and this happens to be the most affected biological process in melasma patients[11]. Chronic UV exposure downregulates lipid metabolism genes, namely peroxisome proliferator-activated receptor alpha (PPAR), arachidonate 15-lipoxygenase, PPAR gamma coactivator 1 alpha, type B (ALXO 15B), diacylglycerol o-acyltransferase 2-like 3 were found to be downregulated[12]. The centro-facial pattern is the principle clinical pattern seen in patients suffering from melasma and is known to occur in 50–80% of the cases, affecting the forehead, nose and upper lip, excluding the philtrum, cheeks and chin. The malar pattern also found in patients afflicted with melasma has hyperpigmentation restricted to the malar cheeks on the face, while mandibular pattern of melasma presents with increased pigmentation present on the jawline and chin of patients. The latter is thought to occur in older individuals and may be more related to severe photodamage in such patients. A newer pattern termed extra-facial melasma can occur on non-facial body parts, including the neck, sternum, forearms and upper extremities[2]. Hydroquinone is considered as the gold standard treatment for melasma. It is a dihydric phenol, it inhibits the tyrosinase enzyme and thereby inhibiting the conversion of dopa to melanin. It also plays a beneficial role in melasma by mechanisms such as inhibition of the synthesis of ribonucleic acid and deoxyribonucleic acid and destruction of melanocytes. A concentration of 2-4% of hydroquinone is used to treat melasma. A combination with other agents enhances the efficacy of hydroquinone, combinations which are common include the Kligman formula (5% HQ, 0.1% tretinoin and 0.1% dexamethasone), modified Kligman's formula (4% HQ, 0.05% tretinoin and 1% hydrocortisone acetate), Pathak's (2% HQ and 0.05-0.1% tretinoin) and Westerhof's formula (4.7% N-acetylcysteine, 2% HQ and 0.1% triamcinolone acetonide)[13]. Tranexamic Acid [TA] is trans-4 -(aminomethyl) cyclohexane carboxylic acid, a lysine analog that is in use as an antifibrinolytic agent for over 30 years. It inhibits UV-induced plasmin activity in keratinocytes by preventing the binding of plasminogen to the keratinocytes. This results in less free arachidonic acid and a diminished ability to produce prostaglandins and this decreases melanocyte tyrosinase activity[14], in treatment of melasma, it is

used in a dose of 250mg twice daily[15]. 4-n-Butyl resorcinol It is a derivative of resorcinol that inhibits tyrosinase and tyrosinase related protein, enzymes in the melanin biosynthetic pathway[16]. A new class of tyrosinase inhibitors have surfaced, these are oligopeptides. They have good efficacy and cytotoxicity figuration. Ubeid et al. conducted a study assessing the inhibitory activity of octapeptides and HQ was assessed and they octapeptides P16-18 outperformed HQ in all categories tested, in addition the oligopeptides showed minimal toxicity toward major human skin cell types[17]. Hantash and Jimenez carried out a pilot study to evaluate the efficacy of an emulsion containing 0.01% decapeptide-12 (Lumixyl cream) in patients with melasma and all patients showed statistically significant improvement with minimal side effects[18,19]. Silymarin, is a polypeptide flavonoid obtained from the milk thistle plant silybum marianum. It's the foremost constituent is silybin (silibinin) that has been established to have antioxidant properties. It mitigates the deleterious effects of UV radiation and also constrains melanin production in a dose-dependent manner[20]. Tretinoin is used extensively in treating melasma in the capacity of over-the-counter lightening agent. Cogitating the virtue of tretinoin, peeling with tretinoin may remediate pigmentation in melasma. Faghihi *et al.* implemented a randomized, double-blinded clinical trial to analyze the utility of 1% tretinoin peel versus 70% GA peel and ascertained that the benefit of 1% tretinoin peel was akin to 70% GA. The patients put forth remarkably lower postprocedure disquiet with 1% tretinoin[21]. Tretinoin can in addition be utilized as a peeling mask. Ghersetich et al. appraised the utility of 10% tretinoin peeling mask using systematized digital photos, mexameter quantification and MASI assessment and they foraged that everyone of the patients evinced moderate or marked boost in all patients using these three parameters bereft of any unpropitious circumstance. The discrepancy in the average MASI score, at baseline and after 10 weeks was 2.9[22]. Obagi blue peel which is put to use in melasma, is assembled at a fixed concentration of trichloroacetic acid (TCA) with a blue peel base. Glycerine, saponins and blue color base that is non-ionic are the integrants of the blue peel base. It abates the surface tension of TCA, water and glycerine and cinches their sedate and homogenous ingress[23]. Amino fruit acid peel is a contemporary peeling impetus being deployed. It is a potent antioxidant and also acts against photopigmentation, having efficacy comparable to glycolic acid and a better side effect profile[24]. An assortment of lasers have been used for treating melasma, these include the following, 1. Green light: Flashlamp-pumped PDL (510 nm), frequency doubled Q switched neodymium: Yttrium aluminium garnet-532 nm (QS Nd: YAG) 2. Red light: Q switched ruby (694 nm), Q switched alexandrite (755 nm) 3. Near-infrared: QS Nd: YAG (1064nm)[25]. The laser most consistently used for treating melasma is the QS Nd:YAG. The fluence exerted is lower than 5 J/cm^2, spot size 6mm, and frequency of 10 Hz. The number of treatment sessions varies from anywhere between 5-10 treatment sessions at 1-week intervals. In recent times, an approach called "laser toning" or "laser facial" has become crescively prominent for the treatment of melasma. This involves the use of a large spot size [6-8 mm], low fluence [1.6-3.5 J/cm^2], multiple passed QS 1064 nm Nd: YAG laser performed every 1-2 weeks for several weeks[26]. Despite the fact that this technique offers good efficacy, adverse effects have also been found to occur. The side effects encompass include hypopigmentation, depigmentation, rebound hyperpigmentation, physical urticaria, acneiform eruption, petechiae and herpes simplex reactivation. A sequential combination of ablative and pigment selective lasers has also been attempted in the treatment of melasma. Ablative lasers clear away the epidermis containing excess melanin., subsequently Q switched pigment selective laser is employed, this can earmark the dermal melanophages. Angsuwarangsee and Polnikorn studied the adequacy of collaborating ultrapulse CO2 laser and Q switched alexandrite laser (QSAL) unaided in six patients with melasma. The site that received combination treatment showed significant response compared with the site that was treated with QSAL alone. However, side effects in the form of contact dermatitis and hyperpigmentation were observed in few patients, especially in those with dark skin. Therefore, only refractory melasma, is treated by collaborating lasers[27]. The objectives of this study carried out by us were to ascertain if a relationship exists between the serum levels of T3, T4, thyroid stimulating hormone (TSH) and melasma and to determine if a link exists between the presence of anti-thyroid per oxidase antibodies and melasma.

MATERIALS AND METHODS

The manuscript has been prepared in accordance with the last update of Helsinki Declaration of 1975, as revised in 2000. Furthermore, we authors should state that their research are in accordance with the ethical measures of the responsible committee and this an observational, cross sectional case control study and we have maintained ethical measures and taken consent from adult research participants. This case-control study was effectuated on 50 females aged 20-50 years with melasma who visited our out patient department and 50 age matched healthy females with no history of melasma as controls were evaluated. The study was carried out over a time span of 6 months time from January 2022 to June 2022 at clinic.

Table 1: Mean Serum Levels of Hormones T3, T4, TSH and Anti TPO in Cases and Controls

Group Statistics

	Group	N	Mean	Std. Deviation		
T3 [ng/ml]	cases	50	1.5288	.07708	11.806	0000<0001
	Controls	50	1.3368	.08534		
T4 [ug/dl]	cases	50	8.3700	.46915	9.592	0000<0001
	Controls	50	9.2700	.46915		
TSH [miu/L]	Cases	50	3.1632	.64112	6.519	0000<0001
	Controls	50	2.2626	.73710		
Anti TPO [iU/ml]	Cases	50	162.5620	21.85920	12.473	0000<0001
	Controls	50	110.9620	19.43871		

Table 2: Comparison of T3, T4, TSH and Anti-TPO Between Groups and within Groups

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
T3 [ng/ml]	Between Groups	.922	1	.922	139.374	.000
	Within Groups	.648	98	.007		
	Total	1.570	99			
T4 [ug/dl]	Between Groups	20.250	1	20.250	92.003	.000
	Within Groups	21.570	98	.220		
	Total	41.820	99			
TSH [miu/L]	Between Groups	20.277	1	20.277	42.494	.000
	Within Groups	46.763	98	.477		
	Total	67.040	99			
Anti TPO [iU/ml]	Between Groups	66564.000	1	66564.000	155.580	.000
	Within Groups	41928.716	98	427.844		
	Total	108492.716	99			

Pregnant women and women who had used drugs which could affect serum level of thyroid hormones in the past 6 months were excluded from this study. Three millilitres of the cases and controls blood was drawn and their sera was collected to be examined for thyroid function tests including T3, T4, TSH and anti thyroid peroxides [anti TPO] antibodies. All tests were carried out using the ELISA method in one laboratory to keep errors and discrepancies at a minimal. Written consent was taken from all the patients before they were enrolled for the study. Data was entered in an excel spread sheet was analyzed using SPSS software. The tests of significance that were carried out were t-test and chi-square test. The P-value<0.05 was considered as statistically significant.

RESULTS AND DISCUSSIONS

The mean age of the patients and the controls in our study was 30.03±6.73 and 32.35±7.8 years, respectively, (P=0.144, t=1.475) which showed no significant difference indicating that the two groups were appropriately matched as regards to age. In 24.7% of the patients and 6.8% of the controls, serum anti-TPO level was higher than normal (P=0.000) which was statistically significant. Serum T3 levels were higher than normal in 75.8% of the patients and 49.1% of the controls (P=0.000), this also happens to be statistically significant. Mean serum TSH levels was found to be 3.16 amongst melasma patients. There was significant difference in the mean level of T3, T4, TSH and anti TPO between patient and control group. (Table 1) showing T3, T4, TSH and anti-TPO levels in cases and controls. (Table 2) showing comparison of serum T3, T4, TSH and anti- TPO between groups and within groups using ANOVA test. In the study carried out by us, mean serum anti TPO levels were found to be 162.56±21.89, which surpassed that reported by Kiani et al who reported 52.08 iu/ml[9]. In this study thyroid auto-immunity was found in 28.9% of melasma patients and 8.9% of controls indicative of a relationship between melasma and thyroid autoimmunity. In the study we conducted, serum anti-TPO levels were found to be higher in 24.4% of the patients and 6.8% of the controls, insinuating a plausible accord between melasma and thyroid autoimmunity. In the present study, serum T3 levels surpassed the normal levels in 75.8% of the patients and 49.1% of the controls and the serum T4 levels were in normal range in 100% of the patients and 100% of the controls. It was established by Kiani *et al*, that the prevalence of thyroid disorders was 3.4 times higher in patients than controls[9]. Lutfi *et al*, conducted a study in which they ascertained that patients with melasma had 4 times higher prevalence of disorders of the thyroid gland as opposed to controls[28]. In the current study, mean serum TSH levels was found to be 3.16 amongst melasma patients. This was higher than that uncovered by Kiani *et al,* who found out that mean TSH levels amongst the melasma patients on whom they carried out the study was 3.05miu/L[9]. There was significant difference between the patients and controls. Melasma as one of the cutaneous attributes of endocrinopathies was apprised by Niepomniszcze and Keterrer[29,30]. Alka Dogre performed a study, in which it was found that 37.5% of the patients suffering from hypothyroidism were also afflicted with pigmentary disorders[31]. In this study implemented by us, higher levels of T3, TSH and

anti-TPO were uncovered and the difference was found to be significant. Nevertheless, we would advocate further studies on melasma patients with contemperoneous disease of the thyroid gland to categorically guage the corollary of treatment of thyroid disorders on the evolution of melasma.

CONCLUSION

Thyroid disorders are frequently found amongst patients suffering from melasma i.e., 76% of melasma cases. Mandibular and malar distribution of melasma are more commonly encountered. Hypothyroidism was the most common thyroid disorder in patients afflicted with melasma with fewer cases of hyperthyroidism being found. 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.

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