Original Article

Assessment of Patients with Periorbital Melanosis for Hyperinsulinemia and Insulin Resistance

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Abstract

Background: Periorbital melanosis (PM) is one of the most common dermatological condition seen in routine practice. Several cutaneous markers such as acanthosis nigricans have been associated with insulin resistance (IR). However, the association of PM with IR needs to be substantiated. **Objective:** The objective of the study is to evaluate the association of circulating adipokines and IR with PM. **Materials and Methods:** In this cross-sectional study, we recruited 100 patients with PM and 100 age- and gender-matched healthy controls. The serum levels of leptin, adiponectin, fasting glucose, fasting insulin, insulin-like growth factor-1 (IGF-1), homeostatic model assessment of insulin resistance (HOMA-IR), and leptin: adiponectin ratio (L/A ratio) were assayed. **Results:** The serum levels of leptin, fasting glucose, fasting insulin, HOMA-IR, L/A ratio were significantly higher in patients with PM as compared to controls. The serum levels of adiponectin were significantly lower in cases as compared to controls. On multivariate regression analysis, leptin, adiponectin, and HOMA-IR were found to be significant, even after adjusting for BMI, blood pressure and LDL and HDL cholesterol.**Conclusion:** Our findings suggest that patients with PM have hyperinsulinemia, IR, and elevated L/A ratio. PM as a marker of IR in adults may help in identifying patients early and thus aid in the early prevention and management of the disease.

Keywords: *Adipokines, adiponectin, insulin like growth factor-1, insulin resistance, leptin, periobital hyperpigmentation*

Introduction

Skin is a major organ system that serves as a window to the changes that happen inside our body and its disorders can sometimes act as a marker for the identification of the underlying disease.[1] Periorbital melanosis (PM) is common dermatological condition that can affect patients of any age and gender. PM is characterized by bilateral hyperpigmentation of the periorbital region that is darker in comparison with the adjoining skin. It is also known by various names such as dark circles, periorbital hyperpigmentation, infraorbital hyperpigmentation, periorbital pigmentation.[2] It is a benign condition with enigmatic pathogenesis. PM can be further divided into two clinical types based on etiology. The first type also known as primary PM manifests as bilateral darkening of the periorbital skin that is not associated with any systemic or local diseases. It is also known as idiopathic cutaneous hyperchromia of the orbital region.

The second type is hyperpigmentation associated with a known cause of systemic or local disease. This condition also worsens with physiological changes associated with aging such as sagging of skin and abnormal lipid deposits around the orbital region.[3] The etiology of PM is multifactorial that include familial, physiological, or associated with chronic illnesses.[4] Various factors that can cause PM includes periorbital melasma, fixed drug eruptions, periorbital acanthosis nigricans, atopy, allergic contact dermatitis, dermal melanocytosis, post-inflammatory hyperpigmentation, shadowing effect due to laxity of periorbital skin and aging. Other environmental causes that can cause PM includes smoking, alcohol, lack of sleep, and stress.[5]

Many cutaneous disorders have been identified as a marker of insulin resistance (IR) that includes acanthosis nigricans, skin tags, hirsutism, and acne.[6,7] IR is characterized by the subnormal response in the uptake of

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glucose by target organs to normal insulin levels and associated with hyperinsulinemia. Hyperinsulinemia can lead to several metabolic consequences such as decrease in levels of sex hormone binding globulin, increase in insulin like growth factor-1 (IGF-1), also causes elevation in levels of leptin, androgen, and insulin like growth factor binding protein 3 (IGFBP-3). These hormones play an active role in the regulation of gene expression required for the proliferation of skin cells which in turn may result in skin manifestations such as acanthosis nigricans and epithelial cell carcinomas.[6,7]

Leptin and adiponectin are protein hormones synthesized mainly from adipocytes. Leptin inhibits hunger by acting on the arcuate nucleus of the brain.[8] In obese patients, there is a decreased sensitivity to leptin, leading to hyperleptinemia which is a marker of metabolic syndrome.[9] Adiponectin, on the other hand, is inversely correlated with obesity and metabolic syndrome.[10] Leptin and adiponectin have opposite actions on inflammation and IR. Leptin increases IR by its pro-inflammatory action, whereas adiponectin has anti-inflammatory properties which can downregulate the pro-inflammatory cytokines.[11] Recently increased leptin: adiponectin ratio (L/A ratio) is also increasingly being used to assess IR among patients with type 2 DM.[12-14]

Some markers such as acanthosis nigricans have been reliable and consistent with the euglycemic clamp test, the gold standard for measurement of IR.[15,16] These cutaneous markers offer several advantages like easy identification, non-invasive, and less time consuming compared to traditional indices for measurement of IR such as Homeostatic Model Assessment (HOMA-IR). A recent study has found that PM is associated with chronic illness such as atopy, anemia, irregular menses, and other post-inflammatory pigmentation disorders including acanthosis nigricans.[4]

There is a possible connection between hyperinsulinemia, associated with IR and PM. Identification of such markers may help general practitioners, family physicians, and dermatologists with a valuable tool in early diagnosis and timely intervention for prevention and management of type 2 diabetes mellitus.There is a lacuna in the literature regarding the association of this extremely common aesthetic condition with IR. Hence, in this study, we evaluated the patients with PM in people above 35 years of age for associated IR and metabolic complications.

Materials and Methods

Setting

This was a cross-sectional study conducted in our hospital, a tertiary care center in South India. This study was done after getting approval from the Institute Ethics Committee (Human studies) (JIP/IEC/2014/1/241).

Study population

Informed consent was obtained from the study participants, before enrollment into this study. Since no previous data was available regarding the problem under investigation, a convenient sample of 100 was taken in each group. Consecutive patients with PM, (aged between 35 and 60 years) attending the Dermatology Clinic of our hospital, were recruited as cases. Age- and gender-matched healthy volunteers without periorbital pigmentation were recruited as controls. The participants were examined by a dermatologist, who verified the diagnosis of PM based on bilateral round or semi-circular homogeneous brown or dark brown pigmentation in the periocular region of the face. Other cutaneous markers of IR were also recorded. Individuals with familial pigmentation, atopy (urticaria, asthma, allergic conjunctivitis, and rhinitis), post-inflammatory pigmentation, erythema dyschromicum perstans, positive shadow effect, dermal melanocytosis, diagnosed/established cases of cardiovascular disease, and morbid obesity-BMI >30 kg/m^2 were excluded from the study.

Assessment of clinical parameters

The clinical characteristics were recorded using standard questionnaire in a predetermined proforma. Age, gender, height, weight, body mass index (BMI), waist circumference, blood pressure, and disease duration were recorded in study subjects.

Grading of PM was done in comparison to surrounding skin as follows: 0 – skin colour comparable to other facial skin areas, 1 – faint pigmentation of infraorbital fold, 2 – pigmentation more pronounced, 3 – deep dark colour, all four lids involved, 4 – grade 3 + pigmentation spreading beyond infraorbital fold.

Assessment of biochemical parameters

Five (5) ml of blood was collected from all study participants, in fasting state. Fasting glucose and lipid profile were estimated using fully automated clinical chemistry analyzer. Fasting insulin, leptin, adiponectin and IGF-1 levels were assayed in serum using commercially available ELISA kits. HOMA-IR formula was used to calculate IR by using fasting insulin and fasting glucose. Leptin: adiponectin ratio was calculated from serum leptin and serum adiponectin levels.

Statistical analysis

All categorical variables were presented as frequencies and percentages. The normality of the continuous data was tested using the Kolmogorov–Smirnov test. Normally distributed data were presented as mean with SD (Standard Deviation) and median with inter-quartile range was used to present the non-Gaussian data. Student *t*-test was used to assess the difference in continuous variables between the two groups.

Association between continuous variables was studied by Pearson correlation. All statistical analysis was carried out using SPSS version 20 at 5% level of significance and *P* value of <0.05 was considered as significant.

Results

One hundred (100) patients with periorbital melanosis and 100 age and gender-matched healthy controls without periorbital melanosis were included in this study. The baseline characteristics are depicted in Table 1. The mean (with SD) duration of disease in patients with periorbital melanosis was 39.75 (± 42.96) months. Among the cases, 31 patients had pigmentation that extended beyond the periorbital region. The clinical characteristics of the cases were given in Table 2. In comparison with healthy controls, the prevalence of some of the risk factors such as photosensitivity, cosmetic usage, pigmentation elsewhere in the body, history of refractive error, sleep deprivation, constant eye rubbing, smoking, alcoholism, and chronic stress were higher in patients with PM [Table 3].

Figure 1a-g shows the comparison of the study parameters between the patients with PM and controls. The serum leptin levels were significantly higher in patients with PM compared to healthy controls. The serum levels of adiponectin were significantly lower in cases as compared to controls. Hence, leptin adiponectin ratio (L/A ratio) was also higher in cases as compared to controls. The serum levels of fasting glucose, insulin and IR, as calculated by HOMA-IR were significantly higher in patients with periorbital melanosis, compared with controls. There was no significant change in the serum levels of IGF-1 between cases and healthy controls [Figure 1a-g]. On multivariate regression analysis, leptin, adiponectin, and HOMA-IR were found to be significant, even after adjusting for BMI, blood pressure, LDL and HDL cholesterol.

Discussion

PM is a common dermatologic condition, although easily diagnosed, cure is not easy.[17] PM is known by various synonyms, and has varied multifactorial etiology. Factors promoting its occurrence can be exogenous as well as endogenous, ranging from ageing lax skin, periorbital oedema, dermal melanocytosis, post-inflammatory hyperpigmentation to periorbital acanthosis nigricans. An Indian study has shown that among Indians, the most common cause of PM is constitutional (51.5%) followed by post-inflammatory (22.5%) and vascular (8%).[2] On the other hand, term facial acanthosis nigricans (FAN) is given to brown to black macular pigmentation with blurred margins, commonly found on the forehead, temporal region, zygomatic, and malar areas with varying degrees of textural changes ranging from mild roughness to frank verrucous appearance of the affected areas of the face.[18] Increased prevalence of obesity, metabolic syndrome, and IR has been documented in such cases.[18,19] Apart from face, acanthosis nigricans has been documented over the neck, axilla, groin, and acral regions in most of these cases. Verma *et al*.[18] also observed periorbital darkening in 17.6% of their FAN cases, however Panda *et al*.[19] noted in 14.6% of cases of FAN. In our study, PM cases without morbid obesity in the age group of 35–60 years were compared with age- and sex-matched controls to look for any association with circulating adipokines and IR to periorbital melanosis.

Periorbital melanosis is one of the most common dermatological condition, whose usefulness as a cutaneous marker remains unexplored till today. Therefore, in the present study, we compared the patients with periorbital

Table 1: Comparison of baseline parameters between cases and controls

Parameters	Cases (*n*=100)	Controls (*n*=100)	*P*
Age (years)	42.27±6.81	43.47±7.38	NS
Gender (F:M)	79:21	79:21	NS
BMI (kg/m^2)	24.49±4.13	22.85±2.77	0.001
Waist circumference (cm)	86.66±20.83	81.79±10.26	0.037
Systolic BP (mmHg)	128.04±7.30	128.10±4.31	0.944
Diastolic BP (mmHg)	79.91±7.55	82.50±5.96	0.008
Total cholesterol (mg/dL)	176.74±32.63	167.59±22.99	0.023
LDL (mg/dL)	113.50±32.90	103.23±24.72	0.013
VLDL (mg/dL)	28.24±7.27	27.56±5.44	0.455
HDL (mg/dL)	35±5.99	36.80±7.91	0.071
Triglycerides (mg/dL)	141.06±35.97	137.73±27.06	0.460

Table 2: Disease characteristics in patients with periorbital melanosis

Parameters	Number of patients
Disease duration (months)	39.75±42.96
Extension beyond periorbital pigmentation	31
Eyelid stretch test	
Improves	96
Worsen	1
No change	3
Direct lighting	
Doubtful shadow persists	1
Shadow disappear	99
Color of pigmentation	
Light brown	30
Dark brown	51
Black	19
Superficial visible vasculature	0
Grade of periorbital pigmentation	
1	26
2	38
3	25
4	11

Table 3: Comparison of risk factors associated with periorbital melanosis between cases and controls

Parameters	Cases (*n*=100)	Controls (*n*=100)	*P*
Family history of periorbital pigmentation	5	0	0.059
Personal history of atopy	4	0	0.121
Family history of atopy	3	0	0.246
Seasonal variation	1	0	1
Photosensitivity	6	0	0.029
Cosmetic usage	23	0	<0.0001
Pigmentation elsewhere in the body	22	0	<0.0001
History of drug intake	9	5	0.280
History of reading for >8 h	5	3	0.721
History of watching television >8 h	18	12	0.322
History of working with computer >8 h	3	7	0.331
History of refractive error	19	1	<0.0001
Sleep deprivation	15	1	<0.0001
History of constant eye rubbing	16	0	<0.0001
History of smoking	7	16	0.034
History of alcoholism	7	22	0.004
Chronic stress	12	0	<0.0001
Premenstrual aggravation	6	0	0.182
Comorbidities	20	0	<0.001
Pallor	1	0	1
Acanthosis nigricans	1	0	1
Pigmentation in other areas of face	3	0	0.246

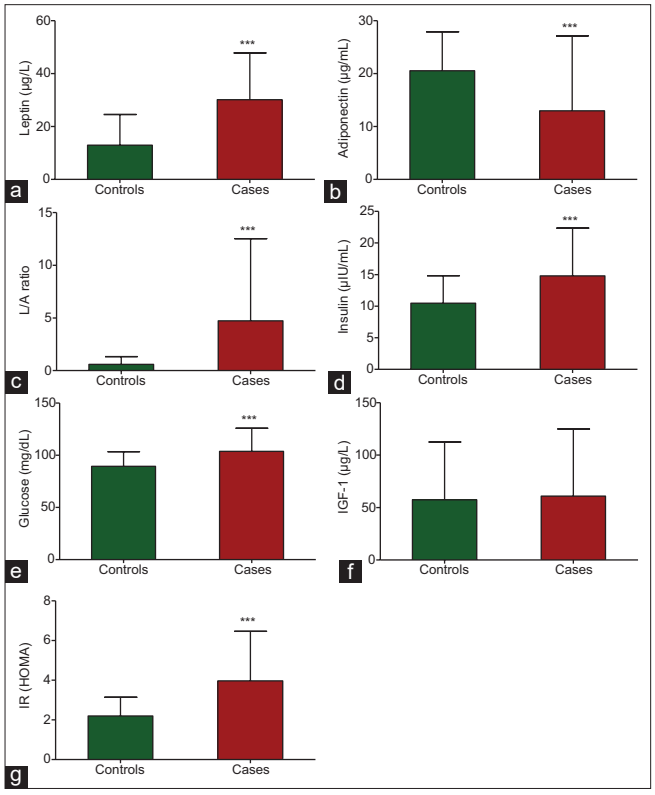

Figure 1: Plasma levels of leptin (a), adiponectin (b), L/A ratio (c), insulin (d), glucose (e), IGF-1 (f), HOMA-IR (g) in patients with periorbital hyperpigmentation (cases) and healthy volunteers (controls). ***$P < 0.001$

melanosis and healthy controls on various parameters related to IR. We found higher levels of leptin, L/A ratio in patients with PM as compared to controls. We also found lower levels of adiponectin in cases as compared to healthy controls. Leptin and adiponectin are two major adipocytokines that play a key role in the regulation of metabolic disorders such as obesity and diabetes mellitus.[20] Leptin plays an important role in the regulation of body weight.[9] Previous studies have shown that higher levels of leptin in obese patients, suggesting resistance to its action by its receptors in the target organs.[11,21] Earlier studies have shown that higher levels of leptin were associated with both BMI and IR.[22-24] Leptin is a pro-inflammatory cytokine with a role in immune response. It induces the production of IL-6, which in turn induces C-reactive protein (CRP) production in the liver.[25] On the other hand, adiponectin was shown to have anti-inflammatory and antidiabetic properties.[26] It was also shown to have a negative correlation with obesity.[27] PM was also reported to be a pro-inflammatory condition and it was shown to have been associated with post-inflammatory causes such as atopic dermatitis and allergic contact dermatitis.[2] Hence our observation is consistent with this hypothesis that PM, being a pro-inflammatory condition would be associated with elevated L/A ratio. In some studies, it has been found in association with FAN.[18,19]

In this study, the levels of fasting insulin, fasting glucose, and IR as calculated by HOMA-IR was higher in patients with PM as compared to healthy controls. There is no significant difference in the levels of IGF-1 in cases as compared to controls. IR occurs due to increased adipocytes, which secretes several cytokines such as leptin, resistin, TNF-α, IL-6, IL-18, all of which are

implicated in the development of metabolic syndrome.[28] It has been reported that hyperglycemia, which is seen in the majority of the patients with IR, develops only at a later stage due to compensatory hyperinsulinemia.[29] Therefore, IR can be regarded as an early subclinical stage in the development of impaired glucose tolerance and diabetes. Identification of patients with IR before the development of clinical signs such as glucose intolerance will provide a potential for early intervention and prevention of diabetes and metabolic syndrome. IR has been shown to have an association with several cutaneous markers in the literature.[16] Previous studies also reported that IR is associated with dermatological disorders such as psoriasis and vitiligo.[1] The most plausible explanation for association of IR with dermatological lesions is that hyperinsulinemia causes increased levels of IGF-1 in keratinocytes and increases their proliferation.[30,31] Our findings also show a significant elevation in fasting glucose, fasting insulin, and HOMA-IR consistent with past observations. But our results failed to show any significant change in the levels of IGF-1 between the PM group and controls. This could be due to the various mechanisms underlying the pathogenesis of periorbital melanosis other than IGF-1, which needs to be further explored.

This study had a few limitations. Though age- and sex-matched controls were taken, but certain variables were distinctly more in case group versus controls. Although there is an association of periorbital melanosis with IR, the etiopathogenesis of PM remains unclear. Further research in this area is required to establish the molecular mechanisms underlying the development of periorbital melanosis and its usefulness as a cutaneous marker for IR.

Conclusion

Our observations indicate that patients with periorbital melanosis have significantly higher levels of leptin, fasting glucose, fasting insulin, L/A ratio and HOMA-IR and lower levels of adiponectin when compared to age and gender-matched controls. PM as a marker of IR in adults (35–60 years) may help in identifying patients early and thus aid in the early prevention and management of the disease.

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Conflicts of interest

There are no conflicts of interest.

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