ABSTRACT:
Gingival pigmentation has intrigued clinicians and researchers alike owing to its numerous etiologies of origin and the difficulties faced in its absolute elimination. The present paper aims to highlight the biochemistry of gingival pigmentation, the common causes and various aspects related to the evaluation of pigmentation. Gingival pigmentation has been defined as the discoloration of the gingiva due to lesions associated with extrinsic and intrinsic factors. Melanin is the most commonly implicated pigment in gingival pigmentation. The biochemistry of melanin pigmentation has been dealt with in detail by several authors and the cells related to the phenomenon i.e. melanocytes, melanophages have been widely studied. Numerous attempts have been made to classify gingival melanin pigmentation. Broadly, lesions have been classified as physiologic and pathologic. Physiologic pigmentation is due to greater melanocyte activity whereas pathologic pigmentation can be due to several causes including endocrine disorders, heavy metal pigmentation, malignancies, so on. Furthermore, for accurate diagnosis and treatment planning, it becomes essential to evaluate the pigmentation in an elaborate and extensive manner. With an increasing demand for esthetics, the diagnosis and treatment of pigmented lesions of the gingiva has gained utmost significance.

Keywords: Gingival pigmentation, Melanin, Melanocytes, Drug induced oral pigmentation

INTRODUCTION:
Gingival pigmentation is a discolouration of the gingiva due to a variety of lesions and conditions associated with several endogenous and exogenous etiologic features. Endogenous pigmentation is caused by five primary pigments viz. melanin, melanoid, oxyhaemoglobin, reduced haemoglobin and carotene. [1] Other cases may be caused by iron and bilirubin. Of all these, the most commonly observed pigment in oral mucosa is melanin.

The gingiva is the most frequently pigmented tissue in the oral cavity. Dummett and Barens implicated many systemic and local factors as causes of changes in oral pigmentation. [2] Various stimuli can result in increased production of melanin including trauma, radiation and medication. Physiologic pigmentation which is the
main condition observed, probably is determined genetically. However, as Dummett suggested, the degree of pigmentation is related part to mechanical, chemical and physical stimulation. High levels of oral melanin pigmentation usually are observed in individuals of African, East Asian or Hispanic backgrounds. [3]

Post-inflammatory pigmentation, smoker’s melanosis, drug related pigmentation are conditions frequently encountered by dentists. Intentional placement of tattoos within the orofacial region is occasionally seen in clinical practice. Clinicians may perform medical tattooing for management of gingival vitiligo. [3]

Although gingival pigmentation is not a pathologic problem, patients usually request cosmetic therapy, particularly if the pigmentation is visible during speech and smiling. Demand for the cosmetic therapy of gingival melanin pigmentation is common. Various methods, including gingivectomy; [4] gingivectomy with free gingival autografts; [5] electrosurgery; [6] cryosurgery; [7,8] chemotherapy with 90% phenol or 95% ethyl alcohol; [9] abrasion with bur; [10] semiconductor diode laser; [11] and CO2 lasers; [12,13] have been used with different degrees of success. Hudelo and Rabut discussed these oral pigmentations and their possible relationship to hereditary syphilis. [14] Prinz published one of the early papers on pigmentations on oral mucous membrane with particular emphasis upon those of pathologic etiology. [15]

**Process of pigmentation**

Fitzpatrick and Lerner discussed the terminology of pigment cells and approved the National Research Council’s adoption of pigment cells nomenclature. [16]

- melanocytes were defined as mature melanin forming cells
- melanoblasts referred to immature melanin forming cells
- macrophages or melanophages were cells that phagocytosed melanin
- melanophores were referred to as contractile cells.

According to the currently followed nomenclature, melanocytes are dendritic cells are located in the basal and spinous layers of the gingival epithelium. They synthesize melanin in organelles called melanosomes. melanophages or melanophores are cells that phagocytose melanin granules. [17]

The process of pigmentation consists of three phases [16]

- Activation of melanocytes
- Synthesis of melanin
- Expression of melanin
I) The activation phase occurs when the melanocytes are stimulated by factors like stress hormones, sunlight etc. leading to production of chemical messengers like melanocyte stimulating hormone.

II) In synthesis phase, melanocytes make granules called melanosomes. This process occurs when the enzyme tyrosinase converts amino acid tyrosine into a molecule called dehydroxyphenylalanine (DOPA). Tyrosinase then converts DOPA into secondary chemical dopaquinone. After a series of reactions, dopaquinone is converted into either dark melanin (eumelanin) or light melanin (pheo-melanin).

III) In expression phase, melanosomes are transferred from the melanocytes to the keratinocytes which are the skin cells located above melanocytes in the epidermis. After this, melanin color eventually becomes visible on the surface of skin.

Major determinant of normal human skin colour is the melanogenic activity within the melanocytes and the quantity and quality of melanin production, but not melanocyte density. The degree of clinical melanin pigmentation in human epidermis and in the epithelium of oral mucosa is related to the amount of melanin i.e. the maturation of melanosomes, the number of keratinocytes containing melanosomes and the distribution of melanin loaded keratinocytes throughout the epithelium.

Classification systems

Numerous classification systems have been given by different authors to classify melanin pigmentation. Dummett et al. classified pigmentation into primary oral, secondary oral, oral non melanin and oral melanoclasis. Brocheriou subdivided lesions into non-tumoral, non-melanin pigmented tumors, benign pigmented lesions and malignant melanoma. Meleti also worked upon classification systems and categorized pigmented lesions into melanin associated and non-melanin associated lesions. An extensive classification was recently put forth by Kauzman et al.

Broadly, gingival pigmentation may be classified as physiologic or pathologic.

Physiologic (ethnic/racial)

All patients except albinos have some degree of physiologic melanin distribution throughout epidermis. Physiologic pigmentation develops during the first two decades of life but may not come to the patients notice until later. Pigmentation is asymptomatic and no treatment is required. Moreover, colour variation may be uniform, unilateral, bilateral, mottled, macular or blotched and may involve the gingival papillae alone or extend throughout the gingiva and into other oral tissues. Eumelanin is present in large amounts in individuals...
with dark skin and hair and is the more photoprotective of the two pigments. Physiologic pigmentation clinically manifests as multifocal or diffuse melanin pigmentation with variable prevalence in different ethnic groups. Common in African, Asian and Mediterranean populations, it is due to greater melanocyte activity rather than greater number of melanocytes. Attached gingiva is the most common site of such pigmentation. [1]

Pathologic gingival pigmentation

a) Endocrine diseases like Addison’s disease, Albright’s syndrome, Acromegaly, Nelson’s syndrome. [17]

b) Heavy metals e.g. lead, bismuth, mercury, silver, arsenic, gold. [17] In children, the possible sources of exposure include lead contaminated water or paint and mercury or silver containing drugs. The pigmentation appears as a blue or black line along the gingival margin and is proportional to the amount of gingival pigmentation. The importance of oral mucosal pigmentation associated with heavy metals lies primarily in the recognition and treatment of the underlying causes to avoid severe systemic toxic effects. [1]

c) Kaposi’s sarcoma – It is the most common malignancy associated with human immunodeficiency virus infection and it may potentially affect every part of the body. Although, palate is the most common site of site of AIDS related Kaposi’s sarcoma, intraoral lesions may also involve the gingiva and other areas. Gingival lesions may extend into the free gingiva and adjacent mucosa or involve the frenum. [22]

d) Drug induced- A variety of medications including chloroquine, quinine, minocycline, zidovudine, chlorpromazine, ketoconazole, bleomycin, cyclophosphamide and so on have been known to cause melanin pigmentation. It can involve accumulation of melanin pigments under the influence of drug or deposition of iron after damage to dermis. Minocycline has also been reported to cause pigmentation of the tongue mucosa. [1] Westerhof et al. reported dark pigmented macular areas on the dorsum of the tongue that they felt was a fixed drug eruption following the inhalation of heroine and methaquinone. [23] Cale et al. reported a case of pigmentation of jawbones and teeth secondary to minocycline hydrochloride therapy. In the present case, it was concluded that the pigmentation was due to gradual, excessive deposition of minocycline within the alveolar bone. [24] Another study by Laporta et al. documented the clinical and histopathologic features of a case of minocycline induced pigmentation of oral soft tissue. Pigmentation of gingiva, lips and nail beds was seen in a patient receiving minocycline therapy. Histopathological examination of biopsy specimens from the gingiva and lips showed evidence of increased melanin/ melanocytes in the
epithelium and melanin/melanophages in the connective tissue. [25]

e) Post-inflammatory pigmentation- Long standing inflammatory mucosal lesions, mainly lichen planus can cause mucosal pigmentation. These are more frequently seen in the dark skinned individuals. Histologically, there is increased production of melanin laden macrophages in the superficial connective tissue. [1]

f) Smoking associated melanosis- Diffuse macular melanosis of buccal mucosa, lateral tongue, palate and floor of the mouth is occasionally seen among smokers. It is probable that in some people melanogenesis is stimulated by tobacco smoke products. No cause and effect relationships have been proved and although most smokers usually fail to show such changes those who do are said to exhibit smoker’s melanosis. Histologically, basilar melanosis with melanin incontinence is observed and the lesions have no malignant potential. [8] Brown and Houston dealt with a case of smoker’s melanosis involving the anterior facial maxillary gingiva. A localized area of melanin pigmentation was seen in the marginal gingiva of a Caucasian female which was excised and subsequently biopsy was performed. Histological analysis showed the lesion to be benign mucosal melanosis compatible with Smoker’s melanosis. [26] Hedin and Larsson studied the morphology of melanosome complexes in gingival epithelium from smokers and non-smokers by electron microscopy. [18]

g) Hemangioma- Vascular lesions presenting as proliferations of vascular channels are tumour like hamartomas when they arise in childhood; in adults benign vascular proliferations are generally varicosities. Depending upon the depth of vascular proliferations, the lesion may have vessels close to the overlying epithelium and may appear reddish, or if a little deeper, blue. [1]

h) Amalgam tattoo- Accidental displacement of metal particles in oral soft tissues during restorative dental procedures using amalgam may result in amalgam tattoo. The cause may be iatrogenic or traumatic. Metal particles may leach into oral tissues and may cause discoloration overtime. Buchner and Hansen listed several iatrogenic and traumatic modalities through which amalgam may be introduced into oral tissues. [27] Bortuluzzi presented a case report of a root perforation sealed with gray MTA that resulted in discoloration of marginal gingiva. [28]

i) Graphite tattoo- Tend to occur on the palate and represent traumatic implantation from a lead pencil. The lesions are unusually macular, focal and grey or black. Microscopically, graphite resembles amalgam in tissue although special stains can segregate the two. [1]

j) Nevocellular nevus and blue nevus- May be found in any age group and seen commonly on palate and gingiva.
Once they reach a certain size, growth ceases and nevus remains stable.

k) Oral melanotic macule- Weather et al introduced the term labial melanotic macule to describe discrete macular areas of hyperpigmentation occurring on lips. Present in up to 3% population, they may range from tan to dark brown in colour, may be irregular in outline and can enlarge up to 1 cm in diameter. The etiology is unclear, though there may be a genetic predisposition. Histological studies show lack of atypia of labial melanotic macule. It may be rarely seen as a component of Loughier-Hunziken syndrome, which has been described as benign areas of macular pigmentation affecting the lips and buccal mucosa in 50% of areas associated with linear streaks of pigmentation on the fingertips.

l) Oral melanoacanthoma- The term was first used to describe a benign mixed skin tumor composed of basal and prickle cell keratinocytes and pigment laden dendritic melanocytes. It is considered to be a reactive process unrelated to the neoplastic melanoacanthoma of the skin. It affects mostly black youngsters, develops quickly and has a flat or slightly raised black to brown surface. These features, together with its tendency to affect mucosal sites exposed to trauma, the observed regression following biopsy or removal of offensive irritants, and the histological features of chronic inflammation favour a reactive nature.

m) Melanoma- Two types are seen, cutaneous and mucosal melanoma

   a) Cutaneous melanomas have jagged irregular margins and are seen on areas that are subject to solar exposure. These show a radial growth phase pattern and have a good prognosis if detected early.

   b) Mucosal melanomas- extremely rare with a higher prevalence in Japanese people. Tend to occur on the anterior labial gingiva and the anterior aspect of hard palate. In early stages appear as brown or black plaques and subsequently becomes more diffuse, nodular and tumefactive.

Takagi et al. presented a review of 120 cases of primary malignant melanoma of the oral cavity occurring in the Japanese. They found an equal sex incidence, peak age of onset at about 50 years and frequent presence of adjacent areas of mucosal melanosis.

The pre-existing melanosis seemed to be the most common pre-cancerous lesion of the oral mucosa as far as
n) Neurofibromatosis - In such cases, a concomitant finding is café-au-lait spots, though oral pigmentation is rarely encountered. [17] Benedict and Fitzpatrick in their study discussed melanotic macules in Albright Syndrome and Neurofibromatosis. The clinical features of the pigmentation in 27 cases of Albright Syndrome and 19 cases of Neurofibromatosis were indistinguishable. The increase in pigmentation in the macules was not necessarily connected with an increase in the number of melanocytes. [34]

o) HIV oral melanosis - Such patients undergo hyperpigmentation of skin, nails and mucous membrane. The etiology of such hyper pigmentation remains undetermined though it may be attributed to medication or adrenocortical involvement by opportunistic parasites. [35, 36] Ficarra et al studied 217 patients seropositive for HIV over 2 years and found that 6.4% developed oral pigmentation. Majority of such patients had multiple macules on the oral mucosa, while labial, palatal and gingival pigmentation were seen in others. [37] Langford et al reported six cases of oral hyperpigmentation in HIV infected patients. While in two patients the lesions could be related to systemic clofazimine or ketoconazole therapy, in the other patients, the cause remained unknown. [38]

p) Haemochromatosis - Patients with haemochromatosis frequently display bluish gray pigmentation of the hard palate, gingiva and buccal mucosa. The pigmentation is caused by deposition of iron containing pigments ferritin and haemosiderin within the skin and mucous membranes. [20]

q) Peutz-Jegher syndrome or peri-orificial lentiginosis, is an autosomal dominant disorder with a high degree of penetrance. It consists of mucocutaneous macules, intestinal hamartomatous polyposis, and increased risk of carcinomas of the gastrointestinal tract, pancreas, breast, and thyroid. The disease is associated with germline mutations in LKB1/STK11 gene located on short arm of chromosome. so called “PTEN hamartoma tumor syndromes”, characterized by mutations in the tumor suppressor gene PTEN (phosphatase and tensin homologue deleted on chromosome 10) include several rare disorders like Ruvalcaba-Myhre-Smith and Cowden syndromes. Peri-oral lentigines have occasionally been reported in these. [20]

r) Cronkhite-Canada syndrome - One of the first defined patients with this syndrome was reported to have ill-defined brown patchy peri-oral and buccal pigmentation in addition to diarrhea, alopecia and diffuse brownish pigmentation of the face, neck and hands. [39]
s) Oral melanocytic pigmentation has been reported in patients with Laughier–Hunziker syndrome and with Carney complex. [40, 41]

t) Gingival tattoo- Rawal et al. reported four cases of cultural practice of gingival tattoo in West African females of three different ethnic groups. Four black females presented with diffuse pigmentation of the maxillary attached gingiva and without any radiographic abnormalities. It was revealed that the women had had one or more sessions of traditional gingival tattooing. Biopsy exhibited dense fibrous connective tissue containing aggregates of foreign material consistent with a foreign body tattoo. [42]

u) Unusual pigmentations of the gingiva- Ashri and Gazi reported three cases of unusual pigmentations of gingival associated with habitual chewing of plants. The first was a brown pigmentation caused by the use of bark of Juglans regia for cleaning of teeth. The second was a bright yellow pigmentation due to chewing of seeds of Cola nitida. The third case reported a mousy brown pigmentation associated with chewing of leaves of Catha edulis. [43]

**Evaluation of oral pigmentation**

When one evaluates a patient who has oral pigmentation, it is imperative to follow a systematic approach to ensure that an adequate assessment has been done. [4]

I. Patients’ history

The history should determine the following

1) Onset of pigmentation- Site onset and duration of lesion should be known.

2) Change in appearance- Any change in colour, size, and appearance since the lesion was first seen.

3) Symptoms- To determine any associated itch, discomfort, pain or bleeding.

4) Other areas of pigmentation- Patient should be questioned for any recent scars or general darkening of skin.

5) Past medical or surgical history- It is essential with reference to systemic diseases and to determine if there was any history of any atypical, unstable or malignant lesion.

6) Drug intake or tobacco use- History of various drugs the patient has been prescribed should be duly taken as these are most potential causes of oral gingival pigmentation.

7) Family history- A positive family history may also predispose a patient to develop oral pigmentation.

II. Clinical examination

Under proper illumination and using a mouth mirror, the following details should be recorded:

1) Number of lesions- may range from solitary to multiple.
2) Distribution of lesions- may be limited to mucous membrane or gingiva or be located on vermilion border of lip or on peri-oral skin.

3) Size, border, colour and uniformity- Colour of lesion, uniformity of pigment, border etc. should be noted along with any evidence of inflammation, surface ulceration and bleeding.

4) Adenopathy- If a malignant lesion is suspected, regional lymphadenopathy should be examined.

5) Distal pigmentation- Pigmentation of scars/sclera or evidence of generalized pigmentation should be evaluated.

III. Investigations

In most cases, a history followed by an adequate clinical examination determines the likely etiology of oral pigmentation. When in doubt, a skin biopsy should be carried out to assess the histological findings to confirm the diagnosis.

Dummett-Gupta Oral Pigmentation Index [44]

Dummett proposed the DOPI (Dummett-Gupta oral pigmentation index) as an epidemiological tool to procure comparative estimates on the occurrence of oral pigmentation throughout various races and nationalities of the world. The index is as follows

- no clinical pigmentation (pink tissue)
- mild clinical pigmentation (mild light brown color)
- moderate clinical pigmentation (medium brown or mixed pink and brown coloration)
- heavy clinical pigmentation (deep brown or blue black tissue)

DOPI assessment = sum of assigned estimates of components  
32 unit spaces

The DOPI assessment is scaled according to following designations

<table>
<thead>
<tr>
<th>Value</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No clinical pigmentation of the gingival</td>
</tr>
<tr>
<td>0.031-0.97</td>
<td>Mild gingival pigmentation</td>
</tr>
<tr>
<td>1.0-1.9</td>
<td>Medium gingival pigmentation</td>
</tr>
<tr>
<td>2.0-3.0</td>
<td>Heavy gingival pigmentation</td>
</tr>
</tbody>
</table>

In recent times, the International Commission on Illumination L * a *b * colour order system is commonly used.
to evaluate coloration of the skin and gingiva in research on melanin pigmentation. In this system, the location of a particular shade in the color scale is defined by three coordinates of L *, a *, and b *, reflecting human colour vision. L * is the vertical axis describing lightness (white is 0 and black is 100), and the two horizontal axes a * and b * indicate red-green and yellow-blue, respectively. [45] Recent studies used L * value to evaluate the degree of melanin pigmentation in skin and gingiva. [46, 47]

CONCLUSION:

Colour of the healthy gingiva is variable ranging from pale pink to deep bluish colour. Between these are several colour variations, dependent upon the intensity of melanogenesis, degree of epithelization, depth of epithelization and depth of gingival vasculature. Over years, attention has been directed to concepts of gingival colour which indicate deep socio-physiological feelings towards oro-mucosal pigmentation. Prevailing attitude towards different gingival colours have been assessed and results indicate significant differences towards different colours of gingiva. [21]

Oral pigmentation may represent a localized anomaly of limited significance or presentation of a potentially life threatening lesion or systemic disease. As such, it becomes imperative for the dental practitioner to be aware of the pathophysiology of the pigmentation of gingiva with particular emphasis upon those of a pathologic etiology.

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