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OROFACIAL PIGMENTATION IN HEMODIALYSIS PATIENTS: A CASE CONTROL STUDY

Radwa R. Hussein[*], Asmaa Abou-Bakr[**], Nevine H. Kheir El Din[*], Ashraf Talaat[***] *and* Eman Khalil[**]

ABSTRACT

Introduction: Orofacial pigmented lesions are one of the most significant changes that present in patients with end-stage renal disease (ESRD), reflecting a wide range of clinical entities ranging from physiologic changes to signs of systemic disorders and even cancers. The research on oral pigmentations is limited, so it is important to pay close attention to this topic. The majority of original publications is either focused on a single lesion or are narrative reports with limited demographic information. As a result, the current study's goal was to determine the incidence of orofacial pigmentation in ESRD patients on hemodialysis in a sample of Egyptian population.

Methods: Case control study design with 262 patients, 131 cases from different hemodialysis centers at Benha Governorate, Egypt and 131 controls from the outpatient clinic of Faculty of Dentistry, Ain Shams University were recruited. The orofacial pigmentation changes were recorded for both groups according to the clinical features and frequencies were calculated.

Results: Orofacial pigmented lesions were present in 115 out of 131 (84.7%) subjects with ESRD, and were present in 25 out of 131 (19.1%) control group with a statistically significant difference between both groups. The most common orofacial pigmentation found in ESRD patients were; abnormal lip pigmentation in 68 patients (51.9%), and petechiae in 37 patients (28.2%).

Conclusions : Since ESRD patients have a high prevalence of orofacial pigmented lesions, mandatory oral screening is required to detect patients with impaired renal function. Healthcare providers should examine the impact of pigmented disorders on health-related quality of life.

KEYWORDS: Egypt, facial, hemodialysis, oral, pigmentation.

* Oral Medicine and Periodontology, Faculty of Dentistry, Ain Shams University, Cairo, Egypt.
** Oral Medicine and Periodontology, Faculty of Dentistry, The British University in Egypt, El Sherouk City, Egypt.
*** Internal Medicine Department, Faculty of Medicine, Benha University, Cairo, Egypt.

INTRODUCTION

Pigmented mucosal lesions are frequent in the mouth, and proper diagnosis can be difficult, since such lesions can be caused by a variety of exogenous and endogenous reasons, including physiologic, reactive, neoplastic, systemic, and idiopathic processes [1]. The degree of keratinization, thickness, vascularization, number and activity of melanocytes, and type of submucosal tissue all influence the color of the oral mucosa [2]. Multifocal or diffuse macular pigmentations, such as physiologic (ethnic) pigmentation, drug-induced melanosis, smoking-associated melanosis, heavy metal pigmentation, and melanosis associated with various systemic diseases, can be classified clinically into focal pigmentations (e.g., oral melanotic macule, amalgam tattoo, melanocytic nevus, melanoma, and melanoacanthoma) [3].

Studies on the frequency of oral mucosal lesions in different populations from both developed and developing nations are abounding in the literature [4, 5]. Only a few studies [6, 7] clearly looked at the relative prevalence of pigmented oral lesions.

One of the most disabling diseases that affects people all over the world is chronic kidney disease (CKD), especially in developed countries where the prevalence of renal disease is high [8]. According to the statistics calculated in Egypt in 2014, the prevalence rate of end-stage renal disease (ESRD) in the governorate of Assiut in upper Egypt was 366 per million population (pmp) [9].

CKD has been defined by the Kidney Disease Improving Global Outcomes (KDIGO) foundation guidelines as the presence of both of these factors (glomerular filtration rate [GFR] less than 60 mL/min and albumin greater than 30 mg per gram of creatinine) along with defects of kidney structure or function for greater than three months. Furthermore, ESRD is defined as a GFR of less than 15 mL/min [10, 11].

There are additional ramifications in the oral cavity of patients with ESRD, which lead to various medical complications as a result of renal failure and many symptoms that occur due to the influence of numerous organs and organ systems in such cases [12].

Ninety percent of patients with CKD exhibit soft tissue alterations and mouth complaints [13]. Some of the uremic oral symptoms mentioned in the literature include mucosal inflammation, mucosal petechiae, ecchymosis, abnormal lip pigmentation, and skin hyperpigmentation [14].

Pigmentary alterations in ESRD patients have been reported in literature as hyperpigmentation, pallor, slate-grey discoloration, and yellow skin hue [15].As renal patients were greatly aesthetically challenged by the abnormal pigmentation of the lip and face [16], and with the increased global burden of chronic renal failure, this highlights the need to identify facial and oral pigmented manifestations in ESRD patients undergoing hemodialysis to assist the clinicians in developing a better approach towards the patients with pigmented orofacial lesions as well as to provide comprehensive information about types, clinical features, and frequency of such lesions for patient reassurance, early conclusive diagnosis and timely treatment.

To the best of our knowledge, this is the first study to assess the frequency of orofacial pigmented lesions in ESRD patients undergoing hemodialysis in a sample of the Egyptian population.

Methods

Study design

This was a case control study involving 262 participants comparing orofacial pigmented lesions in ESRD patients undergoing hemodialysis attending the different hemodialysis centers at Benha Governorate, Egypt with controls from the outpatient clinic at the Faculty of Dentistry, Ain Shams University between October 2021 and January 2022.

Patients selection:

The study group consisted of 131 patients diagnosed with end-stage renal disease according to their GRF less than 15 ml/min. This group was selected from the pool of ESRD patients being managed by different hemodialysis centers at Benha Governorate, Egypt. Patients were on renal hemodialysis from 6 till 24 months, dialysis was performed twice per week and duration of 3 hours per session. The age range was between 30 and 60 years from both genders. The exclusion criteria were smoking, hepatitis C, and patients who will undergo kidney transplantation.

Serum creatinine and blood urea levels were taken from the patient's recent medical record.

Control subjects were 131 medically free subjects. All subjects had a negative history of renal disease or other chronic debilitating illnesses, cigarette smoking, or alcohol intake.

Ethical issues

All procedures were carried out in compliance with the Declaration of Helsinki on Ethical Principles for Medical Research involving human subjects, and approved by Ain Shams University Research Ethics Committee (FDASU-REC) with IRB approval number (FDASU-REC M091810). Patients signed an informed consent after understanding the purpose of the research.

Sample size calculation

A power analysis was designed to have adequate power to apply a statistical test of the null hypothesis that there is no difference would be found between tested groups. By adopting an alpha (α) level of (0.05), a beta (β) of (0.05) (i.e. power=95%), and an effect size (ω) of (0.223) calculated based on the results of a previous study [17]; the predicted sample size (n) was found to be (262) cases (i.e. 131 cases per group). Sample size calculation was performed using PASS 2021 for Windows*.

Clinical Assessment

Patients' demographic data (age, sex, skin color) and medical history included questions about any related skin hyperpigmentation, family history of pigmented disorders, and the presence of systemic signs and symptoms (e.g., fever, malaise, fatigue, weight loss, abdominal pain, gastrointestinal upset). A.A investigated the primary clinical aspects of the lesion, such as the site, time of development, size, symptoms, and color of the lesion, to make a diagnosis of pigmented oral lesions.[18] Patients with orofacial pigmented lesions were also questioned regarding their awareness of the presence of those pigmentations.

Benign pigmented lesions, in general, have regular borders, are small, symmetrical, and consistent in color. They can be flat or elevated. In contrast, malignancy is indicated by uneven boundaries, color change, and surface ulceration.

Skin Color: A subjective assessment of skin color was taken. Individuals were categorized as "white," "brown," or "black" based on a visual evaluation by a research interviewer. The classification took into account the study participants' skin tone as well as their racial origin. The black participants were mostly dark-skinned Egyptians from the Aswan governorate, mostly Nubians.

The extra-oral examination was done by the R.R who performed a meticulous examination of the skin of the face for any change in its color.

Biopsies were taken for patients identified with lichen planus based on clinical signs and symptoms for confirmation. Before the biopsy, all patients gave their consent.

* PASS 2021 Power Analysis and Sample Size Software (2021). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass.

Individual patient's personal data and results had been kept confidential. Patient's names were not shown in the analyzed data; instead, they were encoded by a coding system known by the main investigator only.

Statistical analysis of the data

Categorical data were presented as frequency and percentage values and were analyzed using Fisher's exact test followed by multiple pairwise comparisons utilizing multiple z-tests with Bonferroni correction. Numerical data were presented as mean and standard deviation values and were checked for normality using Shapiro-Wilk test. Data showed parametric distribution and were analyzed using independent t-test. Binomial logistic regression models were used for multivariate analysis. The significance level was set at $p<0.05$ within all tests. Statistical analysis was performed with R statistical analysis software version 4.1.2 for Windows*.

RESULTS

The study was conducted on 262 subjects (i.e. 131 ESRD cases and controls). There was no significant difference between the two groups regarding sex and skin color with p-value 0.528 and 0.155 respectively. On the other hand, there was significant difference between the two groups regarding age where the mean age was 52.96 in the ESRD cases, while it was 39.4 in the control group with $p<0.001$ as in **Table 1.**

There was a significant difference between both groups regarding clinical picture, with significantly higher percentage of controls being free and significantly higher percentage of cases having macules and plaques (with macules being the most prevalent in the cases group) ($p<0.001$). There was a significant difference between both groups regarding lesion color, with significantly higher percentage of controls being free and significantly higher percentage of cases having brown, red/purple or both (with brown color being the most prevalent in the cases group) ($p<0.001$). The most prevalent lesion size was (4-10) mm in diameter and it was 59% in cases and 16.8% in the control group with a statistically significance difference between both groups regarding the lesion size with $p<0.001$. The presence of the orofacial pigmentation in more than one site and on the lip were the most prevalent as regarding the lesion site with 32.5%, 29.8% respectively in ESRD cases with a statistically significance difference between both groups regarding the lesion site with $p<0.001$ as in **Table 2.**

TABLE (1): The demographic characteristics in the cases (ESRD) and control group.

Parameter	Value		Cases	Controls	p-value
Sex	Male	n	82	76	0.528
		%	62.6%	58.0%	
	Female	n	49	55	
		%	37.4%	42.0%	
Age (years)	Mean±SD		52.96± 7.65	39.40± 9.60	<0.001*
Skin color	White	n	19	10	0.155
		%	14.5%	7.6%	
	Brown	n	104	115	
		%	79.4%	87.8%	
	Black	n	8	6	
		%	6.1%	4.6%	

NA: Not Applicable, Values with different superscript letters within the same horizontal row are significantly different *; significant ($p \leq 0.05$)

Table 3 showed that there was a significant difference between both groups regarding the occurrence of petechiae, abnormal lip pigmentation, facial skin hyperpigmentation, lichen planus pigmentosus and orofacial pallor with significantly higher percentage of controls being free and significantly higher percentage of cases being affected ($p<0.05$).

Table 4 represented the different medical history and other biochemical assessment of the ESRD

* R Core Team (2022). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.

TABLE (2): Comparison between cases and control group regarding the different clinical characteristics.

Parameter	Clinical appearance		Cases	Controls	p-value
Clinical picture	Macule	n	101^{A}	25^{B}	<0.001*
		%	77.1%	19.1%	
	Papule	n	2^{A}	0^{A}	
		%	1.5%	0.0%	
	Plaque	n	8^{A}	0^{B}	
		%	6.1%	0.0%	
Lesion color (n=289)	Brown	n	70^{A}	22^{B}	<0.001*
		%	45.2%	16.4%	
	Red/ Purple	n	49^{A}	6^{B}	
		%	31.6%	4.5%	
	Red/ Purple and brown	n	16^{A}	0^{B}	
		%	10.3%	0.0%	
Lesion size (mm) (n=275)	(0-5) mm	n	39^{A}	3^{B}	<0.001*
		%	27.1%	2.3%	
	(4-10) mm	n	85^{A}	22^{B}	
		%	59.0%	16.8%	
Onset	Uncertain	n	24^{A}	25^{A}	<0.001*
		%	18.3%	19.1%	
	After ESRD	n	87^{A}	0^{B}	
		%	66.4%	0.0%	
	No orofacial pigmenation	n	10^{A}	106^{B}	
		%	4.4%	80.3%	
Lesion site (n=360)	Gingiva	n	24^{A}	19^{A}	<0.001*
		%	10.5%	14.4%	
	More than one site	n	74^{A}	0^{B}	
		%	32.5%	0.0%	
	Buccal mucosa	n	16^{A}	1^{B}	
		%	7.0%	0.8%	
	Palate	n	3^{A}	0^{A}	
		%	1.3%	0.0%	
	Floor of the mouth	n	0^{A}	1^{A}	
		%	0.0%	0.8%	
	Lip	n	68^{A}	5^{B}	
		%	29.8%	3.8%	
	Facial skin	n	33^{A}	0^{B}	
		%	14.5%	0.0%	

TABLE (3) Intergroup comparisons regarding the different orofacial pigmentation.

Parameter	Value		Cases	Controls	p-value
Racial pigmentation	***No***	**n**	107	113	**0.400**
		%	81.7%	86.3%	
	Yes	**n**	24	18	
		%	18.3%	13.7%	
Petechiae	***No***	**n**	94^{A}	128^{B}	**<0.001***
		%	71.8%	97.7%	
	Yes	**n**	37^{A}	3^{B}	
		%	28.2%	2.3%	
Abnormal lip pigmentation	***No***	**n**	63^{A}	127^{B}	**<0.001***
		%	48.1%	96.9%	
	Yes	**n**	68^{A}	4^{B}	
		%	51.9%	3.1%	
Facial skin hyperpigmentation	***No***	**n**	98^{A}	131^{B}	**<0.001***
		%	74.8%	100.0%	
	Yes	**n**	33^{A}	0^{B}	
		%	25.2%	0.0%	
Lichen planus pigmentosus	***No***	**n**	123^{A}	131^{B}	**0.007***
		%	93.9%	100.0%	
	Yes	**n**	8^{A}	0^{B}	
		%	6.1%	0.0%	
Ecchymosis	***No***	**n**	128	131	**0.247**
		%	97.7%	100.0%	
	Yes	**n**	3	0	
		%	2.3%	0.0%	
Orofacial pallor	***No***	**n**	59^{A}	131^{B}	**<0.001***
		%	45.0%	100.0%	
	Yes	**n**	72^{A}	0^{B}	
		%	55.0%	0.0%	

NA: Not Applicable, Values with different superscript letters within the same horizontal row are significantly different *; significant (p ≤ 0.05)

TABLE (4) representing the different medical history and biochemical assessment of the ESRD cases group.

Parameter	Value		Cases
Medical history	2ry Hyperparathyroidism	n	5
		%	2.9%
	Autoimmune nephritis	n	1
		%	0.6%
	Cardiovascular disease	n	4
		%	2.3%
	Diabetes mellitus type 2	n	43
		%	24.9%
	Gout	n	1
		%	0.6%
	Hypertension	n	113
		%	65.3%
	Idiopathic renal disease	n	4
		%	2.3%
	Ischemic heart disease	n	1
		%	0.6%
	Recurrent pancreatitis	n	1
		%	0.6%
Duration of hemodialysis (months)	Mean±SD		12.53±6.29
Serum Creatinine (mg/dl)			6.53±1.17
Blood Urea (mg/dl)			134.33±36.60

cases group. The most prevalent medical conditions were hypertension (65.3%) and diabetes mellitus type 2 (24.9%). The mean duration of hemodialysis in the cases group was (12.53±6.29) months, for serum creatinine level it was (6.53±1.17) and for blood urea it was (134.33±36.60).

Table 5 that represented the associations between biochemical and clinical parameters in ESRD cases showed that the occurrence of skin hyperpigmentation and pallor was significantly associated with the increase of hemodialysis duration ($p<0.05$). The occurrence of petechiae was significantly associated with the decrease of serum creatinine ($p=0.039$), while the occurrence of lichen planus pigmentosus was significantly associated with the increase of serum creatinine ($p=0.006$). The occurrence of petechiae and pallor was significantly associated with the decrease of hemoglobin level ($p<0.05$). Controls had significantly higher mean value of hemoglobin than cases ($p<0.001$).

Regression models

Table 6 represented a binomial logistic regression was performed to ascertain the effects of sex, age, duration of hemodialysis, serum creatinine, blood urea and hemoglobin on the likelihood of skin pigmentation occurrence in the cases group. The logistic regression model was statistically significant, $\chi2(6) = 70.07$, $p<0.001$. The model explained 41.4% (Nagelkerke R2) of the variance in skin pigmentation. Of the six predictor variables only duration of hemodialysis was statistically significant ($p<0.001$) with the increase of hemodialysis duration being associated with skin hyperpigmentation occurrence.

Table 7 represented a binomial logistic regression was performed to ascertain the effects of sex, age, duration of hemodialysis, serum creatinine, blood urea and hemoglobin on the likelihood of LP occurrence in the cases group. The logistic regression model was statistically significant, $\chi2(6) = 15.41$, $p=0.017$. The model explained 11.1% (Nagelkerke R2) of the variance in LP. Of the six predictor variables only serum creatinine was statistically significant ($p=0.011$) with the increase of creatinine level being associated with LP occurrence.

TABLE (5) representing the associations between biochemical and clinical parameters among the ESRD cases group.

Measurement	Parameter	(Mean±SD)		p-value
		No	Yes	
Duration of hemodialysis (months)	Skin hyperpigmentation	9.99±3.91	20.09±5.99	<0.001*
	Petechiae	12.02±6.28	13.84±6.22	0.138
	Ecchymosis	12.38±6.23	19.00±7.00	0.072
	Lichen planus pigmentosus	12.49±6.40	13.25±4.68	0.741
	Orofacial pallor	11.29±5.68	13.56±6.62	0.040*
Serum Creatinine	Skin hyperpigmentation	6.58±1.14	6.39±1.26	0.443
	Petechiae	6.66±1.20	6.19±1.03	0.039*
	Ecchymosis	6.54±1.17	6.20±1.56	0.623
	Lichen planus pigmentosus	6.46±1.16	7.62±0.68	0.006*
	Orofacial pallor	6.51±1.11	6.55±1.23	0.863
Blood urea	Skin hyperpigmentation	135.90±37.86	129.69±32.68	0.401
	Petechiae	131.46±38.03	141.64±32.01	0.153
	Ecchymosis	134.27±36.80	137.00±32.60	0.899
	Lichen planus pigmentosus	133.49±34.73	147.25±60.43	0.305
	Orofacial pallor	139.66±32.71	129.97±39.19	0.132
Hemoglobin	Skin hyperpigmentation	8.82±1.66	8.72±1.70	0.760
	Petechiae	9.02±1.61	8.25±1.71	0.017*
	Ecchymosis	8.83±1.67	7.33±0.58	0.124
	Lichen planus pigmentosus	8.86±1.66	7.92±1.64	0.127
	Orofacial pallor	12.97±2.28	7.56±0.90	<0.001*

; significant ($p \leq 0.05$)

TABLE (6) Regression analysis of skin hyperpigmentation.

Variables	Regression coefficient	SE	Wald	Odds ratio	Odds ratio 95%CI		p-value
					Lower	Upper	
Sex (Male)[1]	0.93	0.67	1.90	2.53	0.68	9.49	0.168
Age	0.01	0.04	0.05	1.01	0.93	1.10	0.823
Duration of hemodialysis	0.33	0.05	36.77	1.39	1.25	1.55	<0.001*
Serum Creatinine (mg/dl)	-0.07	0.26	0.06	0.94	0.57	1.55	0.801
Blood urea (mg/dl)	-0.01	0.01	0.84	0.99	0.97	1.01	0.359
Hemoglobin	0.31	0.20	2.50	1.37	0.93	2.01	0.114

SE=Standard error; CI= confidence interval; *; significant ($p \leq 0.05$)

TABLE (7) Regression analysis of lichen planus pigmentosus.

Variables	Regression coefficient	SE	Wald	Odds ratio	Odds ratio 95%CI		p-value
					Lower	Upper	
Sex (Male)[1]	-0.04	0.90	0.00	0.96	0.16	5.65	0.964
Age	0.10	0.07	2.28	1.10	0.97	1.25	0.131
Duration of hemodialysis	0.06	0.06	1.05	1.07	0.94	1.21	0.307
Serum Creatinine (mg/dl)	1.35	0.53	6.55	3.87	1.37	10.90	0.011*
Blood urea (mg/dl)	0.01	0.01	0.84	1.01	0.99	1.03	0.360
Hemoglobin	-0.30	0.27	1.31	0.74	0.44	1.24	0.253

SE=Standard error; CI= confidence interval; *; significant (p ≤ 0.05)

DISCUSSION

Pigmentary disorders are among the top five most commonly diagnosed dermatological problems in Africa [19, 20, 21]. In most cases, the clinical features of pigmented lesions in the oral cavity are adequate for diagnosis [22]. They can express themselves in a variety of clinical patterns, ranging from simple physiologic changes to oral symptoms of systemic illnesses and cancers. The deposition of either endogenous or exogenous pigments as a result of numerous mucosal disorders can cause colour changes in the oral mucosa. Blue/purple vascular lesions, brown melanotic lesions, brown heme-associated lesions, and gray/black pigmentations are examples of pigmentations [23].

Facial skin hyperpigmentation was found in brown colored skin patients with ESRD as brown macules with size ranging from (4-10) mm in diameter in 27 ESRD cases (20.6%) and was in agreement with previous studies [24, 25, 26, 27], and it was relatively low when compared to 54% and 66.33% in other studies [28, 29]. This difference could be attributed to the different selected populations, environmental, genetic, and racial causes. Moreover, when patients were asked about the history of the appearance of the skin pigmentation, they said that those pigmentations did not exist before, and they noticed their appearance at the beginning of their diagnosis of chronic kidney disease.

The present study had shown that skin hyperpigmentation increases with increasing duration of dialysis, which was in accordance with earlier studies [28, 30]. In dialysis-dependent ESRD patients, skin hyperpigmentation is a prevalent clinical characteristic [24]. Middle-molecular-weight substances such urochrome pigments, carotenoids alpha and beta, and melanocyte-stimulating hormone have been connected to the pathogenesis of diffuse pigmentation in ESRD patients [31].

Skin hyperpigmentation is manifested in renal patients is affected by systemic inflammation [32]. As the erythema and pigmentation that occurs in renal patients as a result of ultraviolet B is inhibited by topical anti-inflammatory products, presuming that the pathogenesis of hyperpigmentation that manifested in patients undergoing hemodialysis may be due to the inflammation that occurs [33].

Petechiae was commonly found at 36 (27.5%) ESRD patients, which is consistent with earlier studies [34,35]. However, these results were in contrast to another study reported by ***Belazelkovska et al.*** [12], who reported a much higher prevalence up to 90%. These findings may reflect the underlying increased fragility of the blood capillaries, decreased adhesion of platelets, increased activity of prostacyclin, decreased availability of platelet factor 3, and renal anemia (secondary to deficient erythropoiesis) and related to dialysis, which reduces the count of platelets due to mechanical

damage and heparin anticoagulation during this process [36]. For these reasons, it can be concluded that hemodialysis predisposes to ecchymosis, petechiae, and hemorrhage in the oral mucosa [37].

In a patient with a history of oral lichen planus, postinflammatory pigmentation was found in 8 (6.1%) of ESRD patients, which was consistent with earlier investigations [38, 14]. Lichen planus pigmentosus (LPP) is a disease with an unknown etiology that has an insidious onset and a long course. It is characterized by dark brown macules that appear on the body's exposed parts, although it can also appear on the oral mucosa [39].

An association between serum creatinine and lichen planus pigmentosus was found, and this was in accordance with what was reported by [40]. There is a temporal association of the nephrotic syndrome and oral lichen planus and the flare of lichen planus is coincident with the nephrotic relapse, this may not be a mere coincidence [40]. Furthermore, lichen planus is an immune-mediated condition, and the immune system is involved in the initiation, progression, and resolution of renal disease [41]. This could explain the association between serum creatinine, and lichen planus but the pathogenesis of this association is not clear and needs further study to explain this association. In addition most of the renal patients who undergo hemodialysis suffer from anxiety and depression due to the regular visits of hemodialysis. Anxiety or emotional variables could make lichen planus chronic or influence the emergence of clinical forms that are largely red, symptomatic, and difficult to manage for the doctor, and psychosomatic factors could increase the lesions [42].

Abnormal lip hyperpigmentation was present in 68 (51.9%) of the ESRD patients, and it was reported by only one study [17] with a prevalence of 90%.

The incapability of patients with ESRD to excrete beta melanocyte-stimulating hormone (beta-MSH) via their damaged kidneys resulted in the stimulation of melanocytes that presents at the oral epitheluim's basal cell layer and this leads to abnormal hyperpigmentation in patients with renal impairment [22].

The metabolism of beta-MSH done by the kidneys is not clearly known. As patients undergoing hemodialysis whose kidneys retained to pass little amount of urine, the difference in the levels of plasma of beta-MSH between those with kidneys and those without suggests the non-excretory mechanism that the kidneys could regulate the metabolism of beta MSH. This is supported by the excreted urine that was rich in high amounts of beta-MSH only when plasma levels rise to values much above those of chronic renal failure [43].

There are two possible non-excretory mechanisms: The beta-MSH secretion or metabolism may be controlled by the kidney. The possibility of a pituitary gland stimulation that was explained by the damaged kidney or the retained metabolite in the blood despite dialysis were excluded, as there was a difference in beta-MSH levels in the plasma between patients who had kidneys and those without. Although the possibility of a retained stimulator that is normally destroyed by the kidney is not excluded. Another hypothesis is that there is a factor that is normally produced by the kidney, and this factor inhibits the secretion of beta-MSH from the pituitary gland. In chronic renal failure, this factor production was found to be decreased progressively, and this makes the pituitary gland to secrete a great amount of beta-MSH. This and pituitary stimulation seem unlikely, especially since the high secretion of beta-MSH would generally be related to the adrenocorticotropic hormone (ACTH) high secretion which has not been found in patients with chronic renal failure [44].

Therefore, the most accepted explanation for these abnormal hyperpigmenation is that the major site for the metabolism of beta MSH is the kidney,

and in chronic renal failure the kidneys are damaged, so it leads to impaired metabolism that results in increased levels of beta MSH in the plasma of those patients[45]. The association between high creatinine level and abnormal lip pigmentation that indicates impaired kidney function which was reported in the current study could be explained by these two different mechanisms.

Orofacial pallor was seen in the majority of ESRD patients (76.2%), which is similar to the results published by [12], who found a prevalence of 83.33 %. Anemia in ESRD patients explained the pallor that appeared, which might be linked to the damaged kidney's inability to manufacture erythropoietin, red blood cell loss during dialysis sessions, red blood cell brittleness and early destruction, and nutritional status in these individuals [46]. The low haemoglobin count from the patient's previous record confirmed this, since the participants' mean (SD) haemoglobin levels were 8.80±1.67 in the ESRD subjects.

In conclusion: The frequency of orofacial pigmentation was higher among the cases with ESRD than in control group and the duration of hemodialysis was statistically significant ($p<0.001$) with the increase of hemodialysis duration being associated with skin hyperpigmentation occurrence. Moreover, serum creatinine was statistically significant ($p=0.011$) with the increase of creatinine level being associated with lichen planus pigmentosus occurrence.

Meeting these patients' oral health needs is critical, as early diagnosis by dental professionals is mandatory for early detection of orofacial pigmented lesions especially those with a potentially malignant course. Setting up an integrated oral health intervention with general health care dental practitioners and nephrologists could accomplish this. Further similar researchs in diverse communities around the world are required for a more precise measurement of orofacial pigmentation in ESRD patients.

Limitations: Since the study was conducted on 131 ESRD patients of the total Egyptian population with ESRD copmared with 131 control group, so results cannot be generalized.

Some pigmentations of the oral mucosa can be diagnosed solely on the basis of clinical features and the patient's medical history (for example, racial pigmentation and smoker's melanosis), which may have resulted in an underestimation of the true prevalence of lesions in the current study. In addition, the lack of histpathological biopsies to confirm the diagnosis was regarded as a limitation.

LIST OF ABBREVIATIONS:

CKD: Chronic kidney disease.

ESRD: End-stage renal disease.

SD: Standard deviation.

LPP: Lichen planus pigmentosus.

beta MSH: beta melanocyte-stimulating hormone.

ACTH: Adrenocorticotropic hormone.

Declarations:

Ethics approval and consent to participate:

Approval was obtained from the Ain Shams University Research Ethics Committee (FDASU-REC) with IRB approval number (FDASU-REC M091810).

Individual patient's personal data and results have been kept confidential by filing system with passwords to protect them being preached. Patient's names were not shown in the analyzed data; instead, they were encoded by coding system known by the main investigator only. The study was conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects.

Consent for publication

The procedures were fully explained to all the participants, and they signed an informed consent to share their clinical data for scientific purposes.

Data Availability:

The data that support the findings of this study are available from different hospitals and institutes in Egypt but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data however available from the corresponding author upon reasonable request.

Conflict of Interest:

No conflict of interest exists.

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