INTRODUCTION

Vitiligo is an acquired depigmentary skin disorder due to the loss of cutaneous melanocytes or alteration in their function ***(Richetta et al., 2013)***.Melanocytes loss is the pathological hallmark of vitiligo. Melanocytes dysfunction with decrease of pigment production or donation in keratinocytes could precede true melanocytes loss ***(Boniface et al., 2015).***

The pathogenesis of vitiligo is complex, the exact pathogenesis is not well known. It is a multifactorial disease involving the interplay of several factors ***(Mohammed et al., 2015).***Prevalent hypotheses include the autoimmune, genetic, neural, self-destruction, growth factor deficiency, viral, and convergence theories, which have served as the basis for treatment formulations ***(Hossani- Madani and Halder, 2010).***

In human keratinocytes, the major prostaglandins (PGs) produced are PGE_2, $PGF_{2\alpha}$ and small quantities of prostacyclin (PGI_2) ***(Pentland and Mohoney, 1990)***. In the epidermis, prostaglandin E_2 is released by keratinocytes following ultra violet radiation (UVR) ***(Starner et al., 2010).***

Prostaglandin E_2 stimulates proliferation of human melanocytes, tyrosinase activity and melanocyte dendrite formation ***(Starner et al., 2010).*** It plays an important role in UVR -induced activation of melanogenesis ***(Scott et al., 2007).***

Parsad et al. (2002) and ***Kapoor et al. (2009)*** got encouraging results when they used topical translucent PGE_2 (0.25 mg/kg) gel twice daily for 6 months for the treatment of vitiligo, where many patients showed marked to complete repigmentation of their lesions.

When $PGE_2$was applied to mice skin, there was an increase in melanocyte density, with increased formation of tonofilaments and keratohyline granules in keratinocytes ***(Nordlund et al.,1986).***

Prostaglandin E_2 has stimulative action on the maturation of melanosomes, orientation of microfilaments in the dendrite process, and melanosome complexing in melanocytes of the hair bulb of Caucasians within 24 hours*in vitro****(Parsad et al., 2002).***

A case with an area of vitiligo on upper eyelid margin associated with complete loss of eyelashes and leucotrichia treated with topical application of latanoprost eye drops, repigmentation of vitiliginous patch and the eyelashes was noticed ***(Yadav et al., 2009).***

Aim of the Work

The aim of the work is to evaluate the possible role of PGE_2 in the pathogenesis of vitiligo and its correlation with the disease severity.

VITILIGO

Vitiligo is an acquired, progressive, multifactorial, depigmenting disorder, characterized by the appearance of circumscribed white macules in the skin due to chronic progressive loss of functional melanocytes in the epidermis***(Sandoval- Cruz et al., 2011).***

I-Epidemiology of vitiligo:

Vitiligo occurs worldwide with an estimated prevalence of 0.06%-2.28% in most populations ***(Krüger and Schallreuter, 2012).*** The loss of pigmentation can start at any age during lifetime, and the onset age varies significantly between the studies in different regions of the world. The usual age of onset of vitiligo is between 10 and 30 years. In half of the cases, the disease starts before the age of 20 years and 70-80% of the cases before the age of 30 years ***(Liu et al., 2005).***

Both sexes are equally afflicted by vitiligo. In some studies, a female preponderance has been reported, but the discrepancy can be attributed to a presumed increase in reporting of cosmetic concerns by female patients ***(Wolff et al., 2007).***

The majority of cases ofvitiligo are sporadic without a family history of the disease. Nevertheless, 15-20% of patients report at least one affected first-degree relative. The risk of first degree relatives of patients with vitiligo for developing the disease is elevated by 7 to 10 folds compared to the general population ***(Alkhateeb et al., 2003).***

II- Clinical picture of vitiligo:

Vitiligo lesions present as one or more amelanotic macules or patches that appear chalk or milk white in color, surrounded by normal or hyperpigmented border. Sometimes, the lesions have a red inflammatory border **(inflammatory vitiligo)**. These lesions are of various sizes and shapes. Involvement is oftensymmetrical ***(Yaghoobi et al., 2011).***

Vitiligo lesionsenlarge centrifugally with an unpredictable rate and can involve any body site. Initial lesions appear most frequently on the hands, forearms, feet and face ***(Wolff et al., 2007).*** The most affected sites are face, upper chest, dorsal part of hands, axillae and groin. It has a tendency to involve the skin around orifices. Lesions also appear at trauma sites, a phenomenon called **Köebner phenomenon** (KP) ***(James et al., 2006).***

Vitiligo lesions are hypersensitive to UV light and burn readily when exposed to the sun ***(Yaghoobi et al., 2011).*** Vitiligo is not painful or life-threatening, but its disfiguring manifestation has devastating effect on patient's psychosocial wellbeing ***(Kröger et al., 2011).***Vitiligo patients tend to have higher scores for anxiety, depression, adjust disorders, obsessive symptoms and hypochondria, suggesting a relationship between stress and the development of vitiligo ***(Manolache and Benea, 2007).***

Patients often complain from stigmatization such as curiosity by other people, rejection and discrimination at work, low self-esteem, embarrassment, impaired quality of life, and higher prevalence of sexual difficulties, especially in women ***(Kröger et al., 2011).***

1-Clinical types of vitiligo:

Different approaches have been tried in the classification of vitiligo; however no etiopathogenetic classification has been worked out as a gold standard yet ***(Hercogova et al., 2012).***

Vitiligo can be classified into two subtypes: segmental vitiligo (SV) and non-segmental vitiligo (NSV) ***(Yaghoobi et al., 2011).*** SV is characterized by a dermatomal distribution, earlier onset and rapid progression followed by stabilization ***(Park et al., 2013).*** The etiopathogenesis of SV remains unclear, although several hypotheses have been suggested including mainly neuronal mechanisms ***(Van Geel et al., 2012).***

Patients with SV may also have leukotrichia. Many white hairs in SV may contribute to the lack of response with medical treatment ***(Lee etal., 2011).*** The face is the most common site of SV, other sites as trunk and extremities can be also affected **(figure1)*(Hann et al., 2000).***

Fig. (1): Segmental vitiligo on face ***(Hann et al., 2000)***

The occurrence of SV varies between the studies from 2.5%-27.9% ***(Wang et al., 2013)***.It can appear at any age, but the majority of cases occur early in life between the age of 5 and 30 years ***(Lee et al., 2011)***.Different clinical phenotypes of SV were described including unilateral segmental, bilateral segmental, Blaschkoid, mixed segmental with generalized subtypes ***(Khaitan et al., 2012).***

Non segmental vitiligo is a depigmented skin disorder showing acquired, progressive, and depigmented lesions of the skin, mucosa, and hair. It is believed to be caused mainly by the autoimmune loss of melanocytes from the involved area ***(Arunachalam et al., 2014).*** It is more common and has a potential lifelong evolution. KP and autoimmune diseases are more associated with NSV ***(Lotti et al., 2008; Yaghoobi et al., 2011).*** Both SV and NSV may coexist **(table1)*(Taieb and Picardo, 2007).***

Table (1): Segmental vitiligo versus non segmental vitiligo ***(Taieb and Picardo, 2007)***

	NSV	SV
Prevalence	72-95%	5-28%
Distribution	Symmetrical, non dermatomal	Unilateral,dermatomal
Onset	Any age	Early onset
Course	Variable rate of growth with new lesions through life	Rapid initial growth with non-progression within 2 years
Etiology	Autoimmune	Neurochemical
Köebnerization	Frequent	Rare
Autoimmune association	Strong	Rare

Another classification of vitiligo was established based on distribution and extension of lesions (Nordlund classification).According to this classification, vitiligo is classified into localized, generalized and universal types ***(Nordlund andLerner, 1982; Lotti et al., 2008; Yaghoobi et al., 2011).***

A-Localized vitiligo: is further subdivided into*:*

- **Unilateral:**

One or more macules are localized in a unilateral body region, with a dermatometricdistribution ***(Yaghoobi et al., 2011).***

- **Focal:**

One or more macules with casual distribution, not clearly in segmental distribution. It can be a subset of segmental or generalized vitiligo before the extension***(Taieb and Picardo, 2007).***

- **Mucosal:**

It describes isolated depigmentation of the lips, oral or genital mucosa. Cases of vitiligo with long-lasting focal lesions or of pure mucosal depigmentation may remain simply “unclassifiable” vitiligo **(figure2)*(Ezzedine et al., 2012).***

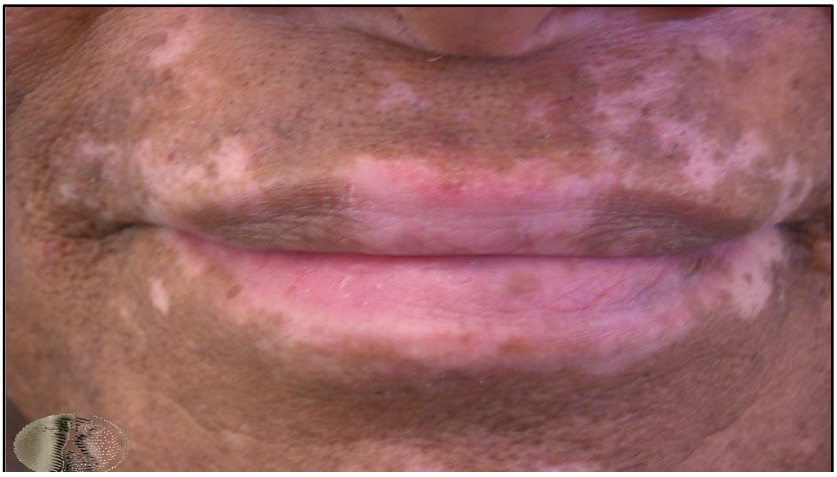

Fig. (2): Mucosal vitiligo ***(Ezzedine et al., 2012)***

<u>B-Generalized vitiligo:</u> is classified into:

- **Acrofacial:**

It is characterized by the presence of vitiligo lesions in the face and extremities **(figure3)*(Wang et al., 2013)*.**

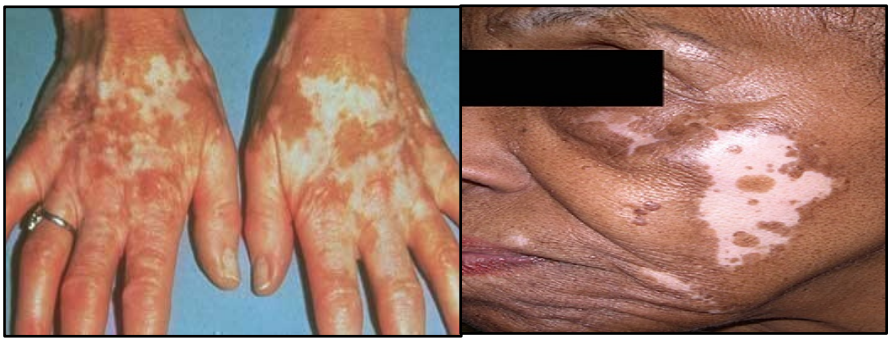

Fig. (3): Acrofacial vitiligo ***(Halder and Chappell, 2008)***

- **Vulgaris:**

Scattered macules extensivelydisseminated**(figure4)** ***(Yaghoobi et al., 2011).***

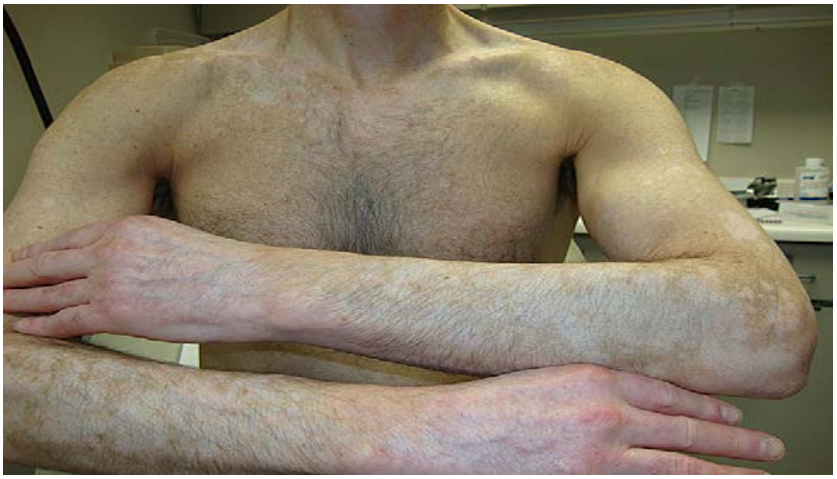

Fig. (4): Vitiligo vulgaris ***(Yaghoobi et al., 2011)***

- **Mixed:**

The mixed type of vitiligo is a quite confusing entity, as it comprises different clinical types of vitiligo at the same time on the patient's body. The number of such cases reported in the literature is too small to understand the real nature of this type ***(Van Geel et al., 2011)*.**

C-Universal vitiligo:

In universal type, nearly complete or complete depigmentation of more than 80% of the body surface appears. This type presents from 0.5% to 18% of the cases of vitiligo **(table2)** ***(Wang et al., 2013).***

Table (2): Clinical types and subtypes of vitiligo***(Torello et al., 2008)***

Type of vitiligo	Subtype	Description
Localized vitiligo	Focal	One or more macules in one area, but not in a segmental distribution.
	Segmental	One or more macules in one area in a segmental distribution.
	Mucosal	Macules only in mucous membranes.
Generalized vitiligo	Acrofacial	Macules on distal extremities and the face.
	Vulgaris	Scattered macules with symmetrical distribution all over the body.
	Mixed	Segmental and vulgaris, segmental and acrofacial, acrofacial and vulgaris.
Universal vitiligo		Complete or nearly complete depigmentation.

Vitiligo Global Issues Consensus Conference classification **(VGICC)** recommends that SV is to be classified separately from all other forms of vitiligo, and the term 'vitiligo' is to be used as an umbrella term for all non-segmental forms of vitiligo, including 'mixed vitiligo' in which SV and NSV are combined and which is considered a subgroup of vitiligo **(table3)** ***(Ezzedine et al., 2012)*****.**

Table (3): Vitiligo Global Issues Consensus Conference classification ***(Ezzedine et al., 2012)***

Type of vitiligo	Subtypes
Non segmental vitiligo	Mucosal (more than one site)
	Generalized
	Universal
	Mixed
	Rare subtypes
Segmental vitiligo	Uni-, bi- or plurisegmental
Undetermined/unclassified vitiligo	Focal
	Mucosal (only one site)

2-Clinical variants of vitiligo:

- **Vitiligo ponctue':** is a rare variant, with discrete confetti-like amelanotic macules occurring on normal or hyperpigmented skin **(figure5)** ***(Ortonne, 2008).***

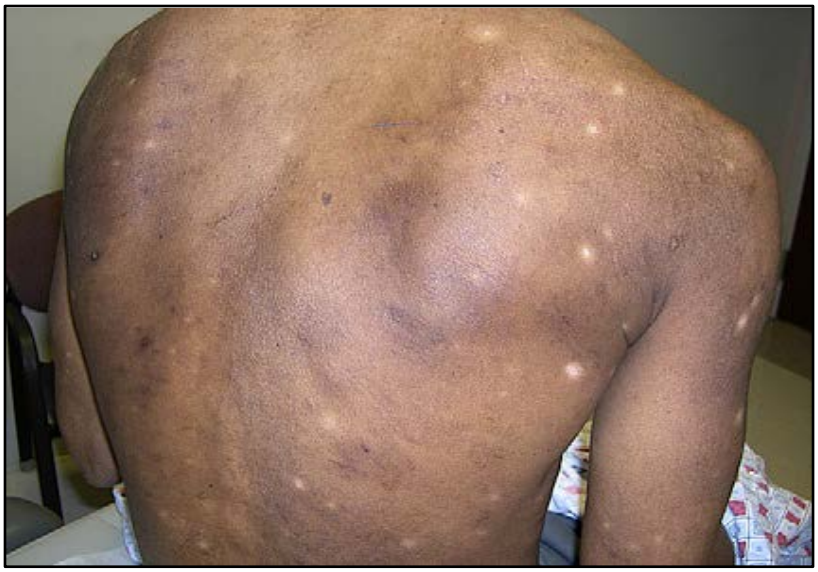

Fig. (5): Vitiligo ponctue' ***(Ortonne, 2008)***

- **Trichrome vitiligo:** has a tan zone between normal and depigmented skin. On histopathology, this intermediate tan zone has more inflammatory cells, langerhans cells (LCs), and melanophages than vitiliginous or normal skin. The number of melanocytes is greater than in vitiliginous skin but less than in normal skin **(figure6)** ***(Hann et al., 2000).***

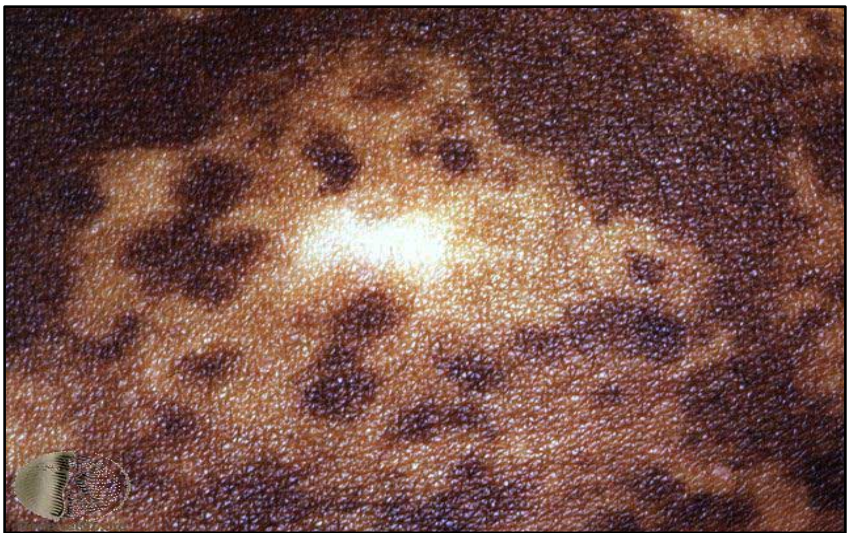

Fig. (6): Trichrome vitiligo ***(Hann et al., 2000)***

- **Quadrichrome vitiligo:** has additional marginal or perifollicular hyperpigmentation. It is more common in darker skin types and in areas of repigmentation ***(Halder and Taliaferro, 2008).***
- **Pentachrome vitiligo**: has been described in black skinned people with variation of five colours: white, tan, brown, blue-gray hyperpigmentation and the normal skin ***(Zhang and Zhu, 2013).***
- **Blue vitiligo:** has a blue-grey hue because of the absence of epidermal melanocytes and the presence of numerous dermal melanophages ***(Chandrashekar, 2009).***
- **Inflammatory vitiligo:** also called "vitiligo with raised inflammatory borders", describes erythema at the margins of depigmentedmacules **(figure7)** ***(Halder and Taliaferro, 2008).***

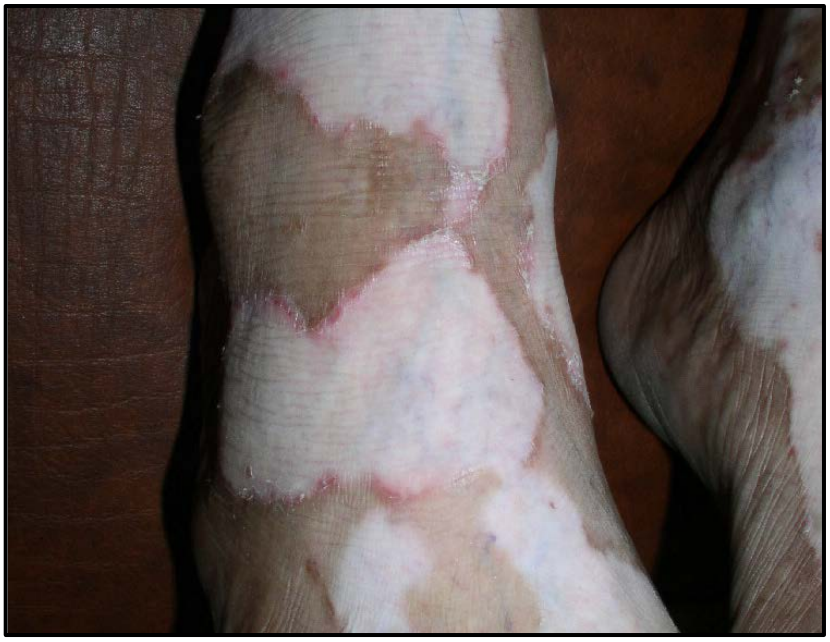

Fig. (7): Inflammatory vitiligo ***(Halder and Taliaferro, 2008)***

3-Associations with vitiligo:

Vitiligo is associated with other autoimmune disorders ***(Birlea et al., 2008)***. Autoimmune thyroiditis is the most prevalent disease associated with vitiligo ***(Boelaert et al., 2010).*** Endocrinopathies, such as Addison's disease, diabetes mellitus type 1, alopecia areata, pernicious anemia, systemic lupus erythematosus, inflammatory bowel disease, rheumatoid arthritis, psoriasis, and autoimmune polyglandular syndrome are also associated ***(Halder and Chappell, 2008).***

Ocular abnormalities are increased in patients with vitiligo, including iritis and retinal pigmentary abnormalities, but patients have no visual complaints. 8% of patients with idiopathic uveitis have vitiligo or poliosis ***(James et al., 2006).***

Auditory abnormalities may associate with vitiligo ***(Aslan et al.,2010)***. The membranous labyrinth of the inner ear contains melanocytes, and the heaviest pigmentation is present in the scala vestibuli.Vitiligo affects all melanocytes, so auditory disturbances may result. Several studies have described familial vitiligo associated with hearing abnormalities and hypoacusis in 16% of patients younger than 40 years who have vitiligo ***(Mahdi et al., 2012).***

Vogt-Koyanagi-Harada disease is a rare systemic T-cell mediated disorder characterized by uveitis, aseptic meningitis, dysacusis, alopecia, poliosis, tinnitus, and vitiligo ***(Igawa et al., 2006).*** Alezzandrini syndrome presents with unilateral facial vitiligo, poliosis, deafness, and retinal degeneration ***(Halder and Chappell, 2008).***

Kabuki syndrome is a rare multiple malformation disorder that is characterized by developmental delay, distinct facial anomalies, congenital heart defects, limb and skeletal anomalies, short stature and vitiligo ***(Ming et al., 2005).***

Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes syndrome is a mitochondrial disorder, that presents with central nervous system abnormalities, neurosensory hearing loss, diabetes mellitus, cardiomyopathy and vitiligo in 11% of cases ***(Halder and Taliaferro, 2008).***

In autoimmune polyendocrinopathy candidiasis ectodermal dysplasia syndrome, patients present with a