Role of Platelet Rich Plasma in vitiligo

Sara Hassan Ahmed 1,Essam Nada1, Reham EzzEldawla 1,Marwa Ali AboElmagd1

Department of Dermatology, Venereology and Andrology

Faculty of Medicine, Sohag University

Abstract:

Vitiligo is a disfiguring disease affecting skin and mucous membranes causing social stigma. Characterised by Milky White patches, due to loss of melanocytes. It remains unclear what causes damage or death to the melanocytes, there are many potential pathophysiological theories involving autoimmune, neural, autocytotoxic, biochemical, oxidative stress, melanocytorrhagy, and decreased melanocyte survival hypotheses.

The exact mechanism of action of PRP in vitiligo is still unknown.The beneficial effect of PRP in vitiligo could be suggested through these growth factors which stimulate keratinocytes and fibroblasts proliferation with subsequent improvement of their interaction with melanocytes leading to the stabilization of melanocytes.

Conclusion

Vitiligo is a common distressing disease with social and psychological effects, new modalities of treatment have been introduced with promising effect of PRP, combined with other treatments

Definition of vitiligo:

Vitiligo is a disfiguring medical disease of unknown origin that causes destruction of melanocytes in the skin, mucous membrane, eyes, inner ear and occasionally hair bulbs. The loss of melanocytes alters both structure and function of these organs and results in absence of pigment *(Drake et al., 1996)*.

Vitiligo is a chronic systemic acquired disease that has an unpredictable clinical course, characterized by the appearance of macules and achromic or hypochromic patches in the affected area. These lesions can appear in different shapes and sizes and may be present in any area of the tegument *(Sharma et al., 2004)*.

Along with the skin and mucosal involvement, melanocytes

in the ocular (predominantly in the uveal tract) and auditory apparatus (in vascular streaking and in the modiolus of the cochlea) can be decreased, ocular diseases such as uveitis or even neurosensory hearing loss may also occur, being detected in 13 to 16% of patients in previous studies (.

However, one of the major consequences of the disease is its psychological impact, since vitiligo can have strong effects on patients' self-esteem, with a subsequent increase in severe depression cases and a sharp sense of social discrimination resulting in quality of life deterioration *(Al-Harbi M., 2013).*

Epidemiology

Vitiligo affects approximately 0.5% to 2% of the population worldwide, and the prevalence appears to be equal between men and women. Although vitiligo occurs worldwide, it is known that its prevalence varies between races and regions*(Allam and Riad, 2013)*.

Abdel-Hafez et al. performed a survey in Upper Egypt and found the prevalence of vitiligo to be 1.2% *(Abdel-Hafez et al., 2003)*. In USA, the prevalence of vitiligo was 0.74%. Other studies have

- 0.5,shown a prevalence of 0.17% in Italy *(Ingordo et al., 2007)*

1% in the French West Indies *(Boisseau-Garsaud et al., 2000)*

In China, several studies have been performed and the ,prevalence of vitiligo ranged from 0.10 to 0.3% *(Li and Xu, 2013)* another population-based and dermatologist-confirmed survey was conducted in 6 cities in China and the prevalence of vitiligo was 0.56% *(Wang et al., 2013)*

Although vitiligo can occur at any age, it is more common in young and middle-aged people. A study reported that the mean age of onset was 18.9 years, while another study found that the mean age of onset was 23.7 years old. Furthermore, it was also reported that vitiligo occurred at 28.4 years old in men and 17.3 years old in women, suggesting that vitiligo occurs earlier in women than in men *(Mchepange et al., 2010)*

Etiopathogenesis

Vitiligo is a common skin disorder characterized by depigmented white patches in the skin due to loss of melanocytes. It remains unclear what causes damage or death to the melanocytes, there are many potential

pathophysiological theories involving autoimmune, neural, autocytotoxic, biochemical, oxidative stress, melanocytorrhagy, and decreased melanocyte survival hypotheses. All of these proposed hypotheses or the pathological mechanisms result in the development of vitiligo.*(Spritz, 2006)*

Autoimmune theory is more prominent in generalized vitiligo, which is considered a complex disorder involving combined pathogenic effects of multiple susceptibility genes and unknown environmental factors that lead to autoimmune destruction of melanocytes.*(Alkhateeb et al., 2003)*.

Moreover, patients with genetic variants (GV) and their close relatives have elevated frequencies of certain other autoimmune diseases suggesting that they have inherited specific diathesis of autoimmune diseases mediated by shared susceptibility genes or in other terms GV is a part of broader genetically mediated autoimmune diathesis *(Spritz, 2006)*

Neural theory is likely to underlie more localized types like segmental and focal vitiligo *(Hann and Lee, 1996)* while melanocytorrhagy may explain the lesions caused by Koebner phenomenon.*(Gauthier et al., 2003)*

The current thought is that vitiligo represents a group of heterogeneous pathophysiologic disorders with a similar phenotype.*(Alikhan et al., 2011)*

The convergence theory states that stress, accumulations of toxic compounds, infection, autoimmunity, mutations, altered cellular environment, and impaired melanocyte migration can all contribute to the pathogenesis. *(Halder and Chappell, 2009)*.

Role of the Immune System

The association of vitiligo with autoimmune conditions is well established. Thyroid disorders, particularly Hashimoto's thyroiditis and Graves' disease, are commonly associated with vitiligo, as are other endocrinopathies, such as Addison's disease and diabetes mellitus.*(Alikhan et al., 2011)*

Alopecia areata, pernicious anemia, systemic lupus erythematosus, inflammatory bowel disease, rheumatoid arthritis, psoriasis, and autoimmune polyglandular syndrome also are associated, though the significance of some of these associations is debated. *(Halder and Chappell, 2009)*

The most compelling argument for an autoimmune pathogenesis is the demonstration of circulating autoantibodies

to melanocytes in the serum of patients with vitiligo. Autoantibodies directed specifically against melanocyte cell surface antigens have the ability to kill melanocytes in vivo and in vitro. The levels of these autoantibodies seem to correlate with disease extent and activity *(Halder and Chappell, 2009)* .

Oxidant-Antioxidant Role in Vitiligo

Oxidative stress may also play an important pathogenic role in vitiligo. Several studies suggest that accumulation of free radicals toxic to melanocytes leads to their destruction. Cultured melanocytes and the serum of patients with vitiligo often have increased nitric oxide levels, suggesting that nitric oxide could lead to autodestruction of melanocytes.*(Hazneci et al., 2005)*

Compared with control patients, the red cells of vitiligo patients have lower levels of glutathione, which helps to prevent free radical mediated injury. Thus, vitiligo patients may be subject to a greater level of oxidative stress *(Hazneci et al., 2005)*

There are at least 5 important pathways enrolled in H_2O_2 overproduction in vitiligo: (1) Defective recycling of 6BH4 (2) Catecholamine formation increased as levels of monoamine oxidase A (MAO) increased (3) Inhibition of thioredoxin/thioredoxin reductase

by calcium (4) NADPH oxidase activities increased by the cellular infiltrate and (5) Nitric oxide synthase (NOS) activities increased.*(Mohammed et al., 2015)*.

Currently, the pathophysiological cause of vitiligo is unclear, and thus, treatment remains challenging. Several treatment options are recommended, including topical and systemic drugs, phototherapy, laser therapy, and surgery, as well as the use of make-up.

The narrow band ultraviolet B (NB-UVB) phototherapy is considered to be a very important modality in vitiligo treatment since its first use in 1997. It was proved to be of higher efficacy, better tolerated, and superior to the other lines of treatment. Nevertheless, it is an office-based treatment that may require more than 1year for its completion. Although success in many cases, some patients may find this long duration of therapy inconvenient due to social and financial reasons *(Nicolaidou et al, 2007).*

The mechanism of action of NB-UVB in vitiligo is through induction of local immunosuppression and stimulation of the proliferation of melanocytes in the skin and the outer root sheath of hair follicles. It has a stimulatory effect on melanogenesis and on the production of Melanocyte Stimulating Hormone (MSH).

Platelet-rich plasma (PRP) is an autologous preparation of platelets in concentrated plasma that is characterized by the presence of several growth factors. Various growth factors, including platelet-derived growth factor, transforming growth factor, fibroblast growth factor, vascular endothelial growth factor, and insulin-like growth factor, are secreted from α-granules of concentrated platelets activated by aggregation inducers *(Kaux et al, 2011)*.

These factors are known to regulate many processes including cell migration, attachment, proliferation, differentiation, and promoting extra cellular matrix accumulation by binding to specific cell-surface receptors. Due to the presence of high concentration of these growth factors, PRP has been used in wide variety of surgical procedures and clinical treatment. *(Ibrahim et al, 2016)*.

The exact mechanism of action of PRP in vitiligo is still unknown. It was reported that not only melanocytes but also keratinocytes and fibroblasts are involved in the pathogenesis in vitiligo in some ways (*Kaux et al, 2011)*. Deficiency in unidentified growth factors as fibroblast growth factor and keratinocyte growth factor may be responsible for weakening of melanocytes attachment and lead to their detachment that cause transepidermal elimination and chronic melanocytorrhagy *(Cho et al, 2012)*.

The beneficial effect of PRP in vitiligo could be suggested through these growth factors which stimulate keratinocytes and fibroblasts proliferation with subsequent improvement of their interaction with melanocytes leading to the stabilization of melanocytes *(Cho et al, 2012)*.

Basic fibroblast growth factor (bFGF) is produced by keratinocyte and act as mitogen on melanocytes in mixed cultures of melanocytes and keratinocytes obtained from untreated vitiligo patients. Zhang et al. demonstrated that bFGF could promote the adhesion and migration of melanocytes, which suggests that it may play a role in the repigmentation of vitiligo. Another study demonstrated that recombinant bFGF significantly enhanced migration of melanocytes through the enhanced expression of phosphorylated focal adhesion kinase on melanocyte *(Seif El Nasr et al, 2011 and Nada et al, 2012)*.

Previous studies found that melanocyte chemokinetic movement induced by bFGF, stem-cell factor, endothelin-1, and leukotriene C4. So that it is believed that these factors may be effective in stimulating vitiligo repigmentation by inducing the proliferation and migration of hair follicle outer root sheath melanocytes into the depigmented epidermis *(Birol et al, 2006)*. Also previous studies demonstrated that b-FGF decreased in vitiliginous area compared with non vitiliginous area (*Nada et al, 2012)*.

References

Abdel-Hafez K, Abdel-Aty MA and Hofny ER: Prevalence of skin diseases in rural areas of Assiut Governorate, Upper Egypt. *Int J* 887-92., 42;*Dermatol,* 2003

Alikhan A, Felsten LM, Daly M and Petronic-Rosic V: Vitiligo: a comprehensive overview Part I. Introduction, epidemiology,

quality of life, diagnosis, differential diagnosis, associations, histopathology, etiology, and work-up. *J Am Acad Dermatol,* 473-91., 65;2011

Al-Harbi M. Prevalence of depression in vitiligo patients. Skinmed, 2013; 11, 327-30

Alkhateeb A, Fain PR, Thody A, Bennett DC and Spritz RA: Epidemiology of vitiligo and associated autoimmune diseases in ;Caucasian probands and their families. *Pigment Cell Res,* 2003 208-14.,16

Allam M and Riad H: Concise review of recent studies in vitiligo. 1-19., 2013;*Qatar Med J,* 2013

Birlea SA, Laberge GS, Procopciuc LM, Fain PR and Spritz RA: CTLA4 and generalized vitiligo: two genetic association studies and a meta-analysis of published data. *Pigment Cell Melanoma* 230-4., 22;*Res,* 2009

Boisseau-Garsaud AM, Garsaud P, Cales-Quist D, Helenon R, Queneherve C and Claire RC: Epidemiology of vitiligo in the , 39;French West Indies (Isle of Martinique). *Int J Dermatol,* 2000 18-20.

rich plasma induces increased -**Cho JW, Kim SA, Lee KS.** Platelet expression of G1 cell cycle regulators, type I collagen, and matrix 1 in human skin fibroblasts. Int J Mol Med -metalloproteinase 6.–32: 29;2012

Drake LA, Dinehart SM, Farmer ER, Goltz RW, Graham GF, Hordinsky MK, Lewis CW, Pariser DM, Skouge JW, Turner ML, Webster SB, Whitaker DC, Lowery BJ, Nordlund JJ, Grimes PE, Halder RM and Minus HR: Guidelines of care for vitiligo. ;American Academy of Dermatology. *J Am Acad Dermatol,* 1996 620-6.,35

Gauthier Y, Cario Andre M and Taieb A: A critical appraisal of vitiligo etiologic theories. Is melanocyte loss a 322-32., 16;melanocytorrhagy? *Pigment Cell Res,* 2003

Halder RM and Chappell JL: Vitiligo update. *Semin Cutan Med*

86-92., 28;*Surg,* 2009

Halder RM, Nandedkar MA and Neal KW: Pigmentary disorders 617-28, vii., 21;in ethnic skin. *Dermatol Clin,* 2003

Hann SK and Lee HJ: Segmental vitiligo: clinical findings in 208 671-4., 35;patients. *J Am Acad Dermatol,* 1996

Hazneci E, Karabulut AB, Ozturk C, Batcioglu K, Dogan G, Karaca S and Esrefoglu M: A comparative study of superoxide dismutase, catalase, and glutathione peroxidase activities and 636-40., 44;nitrate levels in vitiligo patients. *Int J Dermatol,* 2005

Iannella G, Greco A, Didona D, Didona B, Granata G, Manno A, Pasquariello B and Magliulo G: Vitiligo: Pathogenesis, clinical , 15;variants and treatment approaches. *Autoimmun Rev,* 2016 335-43.

Ibrahim ZA, El-Ashmawy AA, El-Tatawy RA, Sallam FA. The effect of platelet-rich plasma on the outcome of short-term narrowband-ultraviolet B phototherapy in the treatment of vitiligo: a pilot study. J Cosmet Dermatol. 2016;15(2):108–116.

Ingordo V, Gentile C, Iannazzone SS, Cusano F and Naldi L: The 'EpiEnlist' project: a dermo-epidemiologic study on a representative sample of young Italian males. Prevalence of selected pigmentary lesions. *J Eur Acad Dermatol Venereol,* 1091-6., 21;2007

Kaux JF, Le Goff C, Seidel L et al. Comparative study of five techniques of preparation of platelet –rich plasma. Pathol Biol 60–157: 59;2011

Kidir M, Karabulut AA, Ercin ME and Atasoy P: Regulatory T-cell cytokines in patients with nonsegmental vitiligo. *Int J Dermatol,* 2017.

Li Y and Xu A: Segmental vitiligo in children: a clinical epidemiologic study in China. *J Eur Acad Dermatol Venereol,* 1056-7., 27;2013

Liu JB, Li M, Chen H, Zhong SQ, Yang S, Du WD, Hao JH, Zhang

TS, Zhang XJ and Zeegers MP: Association of vitiligo with HLA-205, 21;A2: a meta-analysis. *J Eur Acad Dermatol Venereol,* 2007 13.-

Mchepange UO, Gao XH, Liu YY, Liu YB, Ma L, Zhang L and Chen HD: Vitiligo in North-Eastern China: An association between mucosal and acrofacial lesions. *Acta Derm Venereol,* 136-40., 90;2010

Mohammed GF, Gomaa AHA and Al-Dhubaibi MS: Highlights in 221-30., 3;pathogenesis of vitiligo. *World J Clin Cases,* 2015

Nada, Hanan R.a; Rashed, Laila A.b Basic fibroblast growth factor & vitiligo, Journal of the Egyptian Women's Dermatologic Society: January 2012 - Volume 9 - Issue 1 - p 22-25 doi: 10.1097/01.EWX.0000407130.56575.30

Nath SK, Majumder PP and Nordlund JJ: Genetic epidemiology of vitiligo: multilocus recessivity cross-validated. *Am J Hum* 981-90., 55;*Genet,* 1994

Nicolaidou E, Antoniou C, Stratigos AJ, et al. Efficacy, predictors of response, and long-term follow-up in patients with vitiligo treated with narrowband UVB phototherapy. J Am Acad Dermatol 2007; 56: 274–8.

Njoo MD, Spuls PI, Bos JD, Westerhof W and Bossuyt PM: Nonsurgical repigmentation therapies in vitiligo. Meta-analysis 1532-40., 134;of the literature. *Arch Dermatol,* 1998

Rashighi M and Harris JE: Vitiligo Pathogenesis and Emerging 257-65., 35;Treatments. *Dermatol Clin,* 2017

Seif El Nasr H, Shaker OG, Fawzi MM, El-Hanafi G. Basic fibroblast growth factor and tumour necrosis factor alpha in vitiligo and other hypopigmented disorders: suggestive possible therapeutic targets. J Eur Acad Dermatol Venereol. 2013;27(1):103-108. doi:10.1111/j.1468-3083.2011.04368.x

Sharma L, Bhawan R and Jain RK: Hypoacusis in vitiligo. *Indian J* 162-4., 70;*Dermatol Venereol Leprol,* 2004

Spritz RA: Recent progress in the genetics of generalized vitiligo. 271-8., 38;*J Genet Genomics,* 2011

Spritz RA: The genetics of generalized vitiligo and associated 3-10., 41;autoimmune diseases. *J Dermatol Sci,* 2006

Sun X, Xu A, Wei X, Ouyang J, Lu L, Chen M and Zhang D: Genetic epidemiology of vitiligo: a study of 815 probands and 1176-81., 45;their families from south China. *Int J Dermatol,* 2006

Wang X, Du J, Wang T, Zhou C, Shen Y, Ding X, Tian S, Liu Y, Peng G, Xue S, Zhou J, Wang R, Meng X, Pei G, Bai Y, Liu Q, Li H and Zhang J: Prevalence and clinical profile of vitiligo in China: a ;community-based study in six cities. *Acta Derm Venereol,* 2013 62-5.,93

Zhang XJ, Liu JB, Gui JP, Li M, Xiong QG, Wu HB, Li JX, Yang S, Wang HY, Gao M, Yang J and Yang Q: Characteristics of genetic epidemiology and genetic models for vitiligo. *J Am Acad* 383-90., 51;*Dermatol,* 2004