Journal of the Turkish Academy of Dermatology
eISSN 1307-394X

Review

Vitiligo and Oxidative Stress

Zekayi Kutlubay, MD, Tuğba Kevser Uzunçakmak, MD, Burhan Engin, MD, Yalçın Tüzün, MD

Address: Istanbul University, Cerrahpaşa Medical Faculty, Departments of Dermatology, İstanbul, Turkey
E-mail: zekayikutlubay@hotmail.com
** Corresponding Author:* Dr. Zekayi Kutlubay, Istanbul University, Cerrahpaşa Medical Faculty, Department of Dermatology, İstanbul, Turkey

Published:
J Turk Acad Dermatol 2011; **5 (4)**: 1154r1.
This article is available from: http://www.jtad.org/2011/4/jtad1154r1.pdf
Key Words: Vitiligo, Oxidative stress

Abstract

Background: Vitiligo is a chronic, idiopathic, acquired pigmentary disorder which is characterized by depigmented patches on skin and mucous membranes. It affects approximately % 0.1-8.8 of the population. Different hypotheses are concerning to explain etiopathogenesis. Nowadays several studies have been keeping up about oxidative stress in vitiligo etiology. Oxidative stress is the result of overproduction or inadequate removal of reactive oxygen species. Recent studies are mainly major on antioxidants levels and lipid peroxidation product levels in blood. There is not enough evidence about the levels of protein and DNA peroxidation product levels in vitiligo patients. At this point multicentric more studies on larger population are needed to be made to prove the certain affects of these markers in vitiligo etiology.

Introduction

Vitiligo is a chronic, idiopathic, acquired pigmentary disorder which is characterized by depigmente patches in skin and mucous membranes. It affects approximately % 0. 1-8. 8 of the population [1]. Males and females are equally affected and it can develop at any age but approximately half of all vitiligo patients onset is before the age of 20 years [2, 3]. The etiology of the disease is stil not clear. Different hypotheses are concerning to explain this melanocyte activity loss. Most famous theories in pathogenesis are autoimmune theory, cytotoxic theory, biochemical theory, oxidant-antioxidant theory, viral theory, growth factor theory, chronic pressure theory, neural theory and genetic theory [2, 3, 4, 5]. None of these theories have been proved yet. For decades it's accepted that primary pathology in vitiligo is absence of functional melanocytes in vitiligo skin and that this loss of histochemically recognizable melanocytes is the result of their destruction [4]. However, the possibility that melanocytes are still present in vitiligo skin but in an undifferentiated state without melanogenic activity has been proposed [4]. About its genetic pattern although famial clustering of cases is commonly seen, inheritance occurs in a non-Mendelian pattern [3]. Approximately 20 percent of patients with vitiligo have at least one-first degree relative with vitiligo and the relative risk for first degree relatives of vitiligo patients is increased by 7 to 10 fold. The inheritance of vitiligo may involve genes associated with melanin biosynthesis, response to oxidative stress, and regulation of autoimmunity [3].

Oxidative Stress in Vitiligo

Nowadays several studies have been keeping up about oxidative stress in vitiligo etiology. Oxidative stress is the result of overproduction or inadequate removal of reactive oxygen species (free radicals) [6]. This is an imba-

lance toward the pro-oxidant side of the prooxidant/antioxidant homeostasis [7]. The term free radicals has been equated with reactive species or oxidants. By definition, a radical is a molecule possessing an unpaired electron [8,9]. Superoxide, nitric oxide, hydroxyl, alkoxyl and alkyl-peroxyl (lipid) are radicals [9]. These molecules are unstable molecules because of the presence of unpaired electrons. As a result, they can be highly reactive although this varies from radical to radical [8]. Some can react local or any other can donate molecules to other molecules to achieve a more stable state [8]. They can be resulted from many biochemical process within the body including reduction of molecular oxygen during aerobic respiration yielding superoxide and hydroxyl radicals. Oxidation of catecholamines and activation of the arachidonic acid cascade produce electrons, which can reduce molecular oxygen to superoxide; production of superoxide and hypochlorous acids by activated phagocytes. Also they can be generated in the body in response to electromagnetic radiation from the enviroinment and acquired directly as oxidizing pollutants such as ozone and nitrogen dioxide [8].

As most molecules are not free radicals, the majority of reactions will involve nonradicals. Reaction of a radical with a nonradical produces a free radical chain with the formation of new radicals, which in trun can react with further macromolecıules [8]. Target macromolecules include lipids, proteins, nucleic acids and carbohydrates.

In a healthy body these oxidant molecules are cleared off by the antioxidant systems. These defences can be conveniently considered as cellular, membrane, and extracellular mechanisms. Cellular anti oxidant defences include the dismutase, peroxidase and catalase enzymes [8]. Superoxide dismutase (SOD) in cytosol and in mitochondria catalyses the dismutation of superoxide to hydrogen peroxide and oxygen [8, 9]. Beta carotene, ascorbic acid, tocopherol, uric acid, glutation, coenzyme Q, metallotionin and ferritin are major antioxidants. Vitamin E, β-carotene and coenyzme Q are antioxidants which are low molecular weight and present within the cell membrane. Lipophilic vitamin E is a highly effective anti oxidant when in the lipid core of cell membranes. Tocopherol is a much less reactive and is converted back to a alpha tocopherol by vitamin C [8]. Its mainly role is to prevent the lipid peroxidation and reduce the oxygen density in lipid compartment [8]. Glutation is an important cofactor of antioxidant enzymes [6]. Also membrane cholosterol and phospholipids are important for free radical attacks [8]. If any deficiency happens in these systems then accumulation of these species occurs. Accumulation of reactive oxygen species leads to lipid peroxidation, DNA mutation or breakage, enzyme activation or inactivation, protein oxidation [6]. These reactions cause functional loss, genetic mutations and autodestruction in organism and tissue injury. Severe oxidative stress results in necrotic cell death [9]. Overall, the inherent ability of cells to withstand oxidative stress is dependent upon several factors: their antioxidant capacity, the ability to sustain metabolic requirements by deriving energy from alternate pathways, efficiency to repair oxidatively modified biomolecules, and availability and utilization of trophic support [9].

These oxidation reactions features as various clinical diseases pathogenesis by many different pathways. Most important examples are lipid oxidation and protein oxidation, eg. addition of carbonyl groups or crosslinking of fragmentation, carbonyl derivates of amino acid residues from proteolysis. Lipid peroxidation has a potential importance especially in vascular damage and in melanocyte destruction in vitiligo [8].

In several dermatological diseases, oxidative stress effect can be observed as skin cancer, vitiligo, psoriasis, akne vulgaris, skin ageing, atopic dermatitis, *Behçet*'s disease, hyperhydrosis, contact dermatitis [6]. In vitiligo oxidative stress and accumulation of free radicals in the epidermal layer of affected skin have been shown to be involved areas. To prove the effect of these species on affected skin they can be measured in blood or revealed by histologically. The short half life of most reactive species in biological systems does not permit for their direct detection and quantification [9]. Biological targets that have been utilized for detection of oxidative modification include lipids, proteins, thiols and DNA [9]. Reactive species reacts with more than one biological target and since the concentration of biological targets varies among cells, it is difficult to predict which target will be preferentially modified. Therefore, in more complex systems, it

Table 1. Common Biomarkers of Oxidative Stress Used in the Study of Human Diseases

Lipid
Chlorinated/nitrated lipids (isoprostanes, isoleukotriens)
Oxysterols (Aldehyde)
Peroxides (Malondialdehyde, 4-hydroxy-2-nonenal, acrolein)
Protein
Aldehyde adducts
Carbonyl group formation
Nitrated/chlorinated Tyr, Trp, Phe
Oxidised Tyr, Trp, His, Met, Lys, Leu, Ileu, Val
Protein peroxides/hydroxides
SH (thioloxidation)

may be necessary to measure more than one end-point modification of biological targets. For example, measurement of the reduced to oxidized glutathione ratio will reflect a degree of oxidative stress but will not be useful in elucidating potential pathways responsible for the oxidation [**9**] (**Table 1**).These markers can be measured with different methods like spectrophometric assay, ELISA, *Western* blot immunoassay.

Recently clinical studies major on mainly superoxide dismutase (SOD), catalase (CAT), glutatione peroxidase (GPx), nitric oxide (NO) and malondialdehyde (MDA). Different results are reported about the levels of these biomarkers. Some researchers reported high levels of oxidants and antioxidants, some found no difference between patients and controls, some reported low levels of these markers. While *Yıldırım* et al. [**10**], *Dammak* et al. [**11**] and *Sravani* et al. [**12**] reported high levels of SOD, glutation peroxidase and malondialdehyde and low levels of catalase levels [**10, 11, 12**] in vitiligo patients, *Koca* et al. and *Akrem* et al reported low levels of SOD, catalase and GPx in their study [**2, 13**]. *Schallreuter* et al. also reported low catalase levels and high levels of hydrogen peroxide (H_2O_2) in vitiligo patients' involved skin [**14**]. *Picardo* et al. [**15**] and *Passi* et al. [**16**] found no difference in blood levels of SOD, GPx, lipoperoxidase, vitamin E and ubiquinone. *Eskandani* et al. reported negative correlation between levels of systemic oxidative stress and of tyrosinase activity [**17**]. *Boisseau-Garsaud* et al. investigated total anti-oxidant status in vitiligo, examined blood levels of selenium, ferritin, transferrin, ceruloplasmin, retinol and tocopherol [**18**]. They found no difference in levels of ferritin, transferrin, ceruloplasmin, retinol and tocopherol between vitiligo patients and healthy controls and increased level of selenium in vitiligo patients [**18**].

Even though all these studies have different results they confirm the imbalance in prooxidant/ antioxidant systems in vitiliginous skin. Recently studies are mainly major on antioxidants levels and lipid peroxidation product levels in blood. There is not enough evidence about the levels of protein and DNA peroxidation product levels in vitiligo patients. At this point multicentric more studies on larger population are needed to be made to prove the certain effects of these markers in vitiligo etiology.

References

1. Arican O, Kurutas EB. Oxidative stres in blood of patients with active localized vitiligo. Acta Dermatoven APA. 2008; 17: 12-16. PMID:18454264
2. Koca R, Armutcu F, Altinyazar HC, Gurel A. Oxidant-antioxidant enzymes and lipid peroidation in generalized vitiligo. Clin Exp Dermatol 2004; 29: 406- 409. PMID:15245542
3. Halder RM, Taliaferro SJ. Vitiligo. In: Fitzpatrick's Dermatology in General Medicine. Wolff K, Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, eds. 7th Ed. New York: Mc- Graw Hill Companies, 2008; 616-622.
4. Ortonne JP. Vitiligo and other disorders of hypopigmentation. In: Dermatology. Bolognia JL, Jorizzo JL, Rapini RP, Horn TD, Mascaro JM et al, eds. Spain: Mosby, 2003; 947-955.
5. Schallreuter KU, Bahadron P, Picardo M, Slominski A, Elassiuty YE et al. Vitiligo pathogenesis: autoimmun disease,genetic defect, excessive reactive oxygen species, calcium imbalance or what else. Exp Dermatol 2008, 17: 139-160. PMID:18205713
6. Karaca Ş, Güder H. Dermatolojide antioksidan sistem. Turk J Dermatol 2009; 3: 32-39.
7. Dalle-Donne I, Rossi R, Giustarini D, Milzani A, Colombo R. Protein carbonyl groups as biomarkers of oxidative stress. Clinica Chimica Acta 2003, 329: 23-38. PMID:12589963
8. Betteridge J. What is oxidative stress. Metabolism 2000, 49: 3-8. PMID:10693912
9. http://blog. targethealth.com
10. Yildirim M, Baysal V, İnaloz HS, Can M. The role of oxidants and antioxidants in generalized vitiligo at tissue level. JEADV 2004, 18: 683-686. PMID: 15482295
11. Dammak I, Boudaya S, Abdallah FB, Turkı H, Attia H, Hentati B. Antioxidant enzymes and lipid peroxidation at tissue level in patients with stable and active vitiligo. Int J Dermatol 2009, 48: 476-480. PMID: 19416376

12. Sravani PV, Babu NK, Gopal GRR, Rao AR, Moorthy B, Rao TR. Determination of oxidative stres in vitiligo by measuring superoxide dismutase and catalase levels in vitiliginous and non-vitiliginous skin. Indian J Dermatol Venereol 2009, 75: 268-271. PMID: 19439879

13. Jalel A, Yassine M, Hamdaoui MH. Oxidative stres in experimental vitiligo C57BL/6 mice. Indian J Dermatol 2009, 54: 221-324. PMID:20161850

14. Schallreuter KU. Successful treatment of oxidative stres in vitiligo. Skin Pharmacol Apps Skin Physiol 1999, 12: 132-138. PMID:10393521

15. Picardo M, Passi S, Morrone A, Grandinetti M, Di Carlo A, Ippolito F. Antioxidant status in the blood of patients with active vitiligo. Pigment Cell Res 1994, 7: 110-115. PMID:8066016

16. Passi S, Grandinette M, Maggio F, Stancato A, De Luca C. Epidermal oxidative stres in vitiligo. Pigment Cell Res 1998, 11: 81-85. PMID:9585244

17. Eskandani M, Golchai J, Pirooznia N, Hassannia S. Oxidative Stress level and tyrosinase activity in vitiligo patients. Indian J Dermatol 2010, 55: 15-19. PMID:20418970

18. Boisseau- Garsaud AM, Garsaud P, Lejoly-Boisseau H, Robert M, Quist D, Arveiler B. Increase in total blood antioxidant status and selenium levels in black patients with active vitiligo. Int J Dermatol 2002, 41: 640-642. PMID:12390184