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The Potential Role of Hyperbaric Oxygen Therapy in Psoriasis Treatment: A Review of PI3K/AKT/FOXO Signaling Cascade and Interleukin-1β

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ABSTRACT

Psoriasis is a chronic, immune-mediated inflammatory skin disorder that affects 2-3% of the population worldwide. Current therapies, including biologic agents, often have adverse effects and incomplete efficacy. Recent studies suggest that the PI3K/AKT/FOXO signalling cascade and interleukin-1 β play a crucial role in the pathogenesis of psoriasis. Hyperbaric oxygen therapy, a safe and well-tolerated procedure, has been suggested as a potential treatment for psoriasis due to its ability to increase tissue oxygenation and reduce inflammation. This review article summarizes the current understanding of the pathophysiology of psoriasis and the potential benefits of hyperbaric oxygen therapy as a treatment modality. The authors suggest that hyperbaric oxygen therapy may modulate the PI3K/AKT/FOXO signalling cascade, reduce interleukin-1 β levels, and improve skin oxygenation, leading to the attenuation of psoriatic plaques. Further clinical studies are needed to confirm the safety and efficacy of hyperbaric oxygen therapy in psoriasis treatment.

KEYWORDS: psoriasis, hyperbaric oxygen therapy, PI3K/AKT/FOXO signaling cascade, interleukin-1 β

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INTRODUCTION

Psoriasis is a common, chronic, remitting and relapsing, immune-mediated hyperproliferative inflammatory skin disorder with a strong genetic predisposition that affects 2–3% of the population in the world and is associated with a reduced quality of life and a shortened life expectancy due to the association with the metabolic syndrome and cardiovascular pathologies.[1] Clinically psoriasis presents with red, scaly plaques, which mostly affect predilection sites such as extensor surfaces of forearms and shins, umbilical, perianal, retro-auricular regions, and scalp. These plaques are characterized by epidermal hyperproliferation with impaired keratinocyte differentiation, extravasation of lymphocytes, and angio(neo)genesis.[2]

PATHOPHYSIOLOGY OF PSORIASIS

Although the pathogenesis of psoriasis is still not fully understood, currently the dysregulation and amplification cycle of keratinocyte activation and inflammation is a Hallmark of psoriasis pathology. It is assumed that sustained activation of plasmacytoid dendritic cells by epidermal antigens due to skin trauma or infection is the first step in the pathogenesis of psoriasis.[3] Such event induces the maturation of myeloid dendritic cells, which in turn promote the differentiation of T cells into T-helper type 1 (Th1) and T-helper type 17 (Th17) cells via secretion of interleukin-6 (IL-6), interleukin-12 (IL-12), and interleukin-23 (IL-23).[4]

The effector cytokines of the T-helper cells such as interleukin-17 (IL-17), interleukin-22 (IL-22), and TNF-α induce and maintain hallmarks of psoriasis such as keratinocyte proliferation, and disturbed differentiation, leading to epidermal acanthosis, hyperkeratosis, and parakeratosis.[5] Activated keratinocytes in turn produce important proinflammatory cytokines and chemokines that are able to recruit a broad spectrum of inflammatory cells from the vascular system. Thus, a “vicious circle” of excessive immune response, epidermal hyperproliferation,

and neovascularization is initiated, which leads to the complex clinical appearance of psoriasis.[6]

PI3K/AKT/FOXO signalling cascade

The forkhead box (FOX) proteins are a family of transcription factors that play important roles in regulating the expression of genes involved in growth, proliferation, differentiation, and longevity of the cells. Members of the class O (FOXO) regulate metabolism, proliferation, stress tolerance and possibly lifespan of cells. This FOXO transcription factors are negatively regulated by the PI3K/AKT signaling pathway and considered to have inhibitory effect on cell proliferation. Transcription factor proteins are downstream targets of the signalling pathways. One of the signalling pathways is phosphatidylinositol 3-kinase (PI3K) and protein kinase B (AKT) signaling pathway, which play a vital role in cell proliferation and survival. Phosphatidylinositol 3-kinase (PI3K) signalling regulates proliferation of keratinocyte by activating protein kinase B (AKT), and by inducing the forkhead box O (FOXO) downregulation. In psoriatic lesions, the amplification of PI3K and AKT signalling activity and the loss of the FOXO are detected.[7]

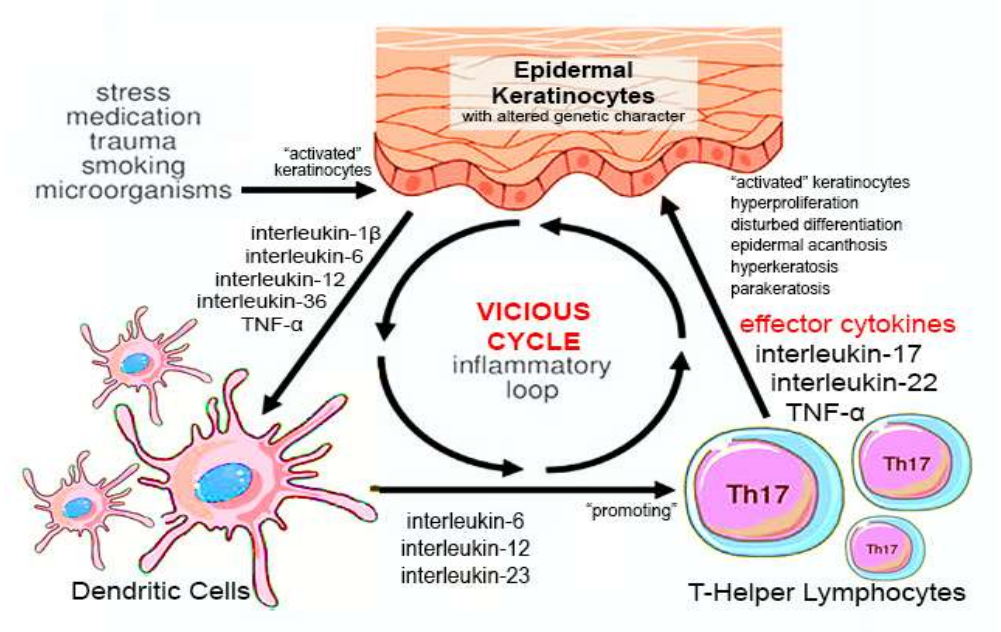

Figure 1. Vicious cycle of inflammatory loop in pathophysiology of psoriasis vulgaris

Interleukin-1 β

A highly inflammatory cytokine, Interleukin-1 β has been linked to psoriasis. Interleukin-1 β is predominantly produced by monocytes, dendritic cells (DCs) and macrophages; additionally keratinocytes also produce Interleukin-1 β in lesser amount. There is evidence that interleukin-1 β stimulates the recruitment of PI3K to the receptor * as a result interleukin-1 β plays a vital role in the PI3K/AKT signalling pathway and consequently amplifies the proliferation rate of keratinocytes.[8]

Current therapy for psoriasis

Current topical therapies used to manage psoriasis include steroids, vitamin D derivatives, retinoids, immunosuppressants, anthralin, coal tar ointment, and several other agents.[9-13] These drugs often have adverse effects that may be poorly tolerated. Light therapy includes ultraviolet B phototherapy or psoralen and ultraviolet A (PUVA) photochemotherapy. However, increased rates of non-melanoma skin cancer have been observed following PUVA therapy.[14] Systemic therapies for psoriasis include methotrexate, cyclosporine, oral retinoids, and biologic therapies. A recent report reviewed the effectiveness and safety of the biologics alefacept, efalizumab, etanercept, and infliximab for managing psoriasis.[15] In addition to the reported adverse effects of the drugs, it was found that up to 40% of patients did not use their medication as directed.

Hyperbaric oxygen therapy

Hyperbaric oxygen therapy is defined as breathing pure (100%) oxygen under conditions of increased atmospheric pressure. This results in elevated arterial oxygen tension to 2,000 mmHg or greater, which provides tissues with abundant amount of oxygen. Possible complications of hyperbaric oxygen therapy therapy include barotrauma, oxygen toxicity (affecting the central nervous system and lungs), claustrophobia and anxiety, and ocular effects such as myopia and cataract. hyperbaric oxygen therapy promotes proliferation of fibroblasts, epithelial cells, and blood vessels in a wound. It can increase the killing ability of leukocytes and is lethal to certain anaerobic bacteria. Furthermore, it inhibits toxin formation by certain anaerobes, increases the

flexibility of red cells, reduces tissue edema, and conserves intracellular ATP. The Undersea and hyperbaric Medical Society and the Federal Center for Medicare and Medicaid Services have approved the use of hyperbaric oxygen therapy in 14 indications including gas gangrene, necrotizing soft-tissue infections, diabetic foot ulcer, compromised grafts and flaps, bone infection, intracranial abscess, anemia and blood loss, crush injury, carbon monoxide and cyanide poisoning, radiation complications, decompression sickness, and gas embolism.

Hyperbaric oxygen therapy has potential effects on mediators of inflammation and the immune response. Several reviews[16,17] support the contention that hyperbaric oxygen therapy has anti-inflammatory and immunosuppressive properties. hyperbaric oxygen therapy also decreases the interleukin-1β activity that later decreases both phosphatidylinositol 3-kinase (p-PI3K) and protein kinase B (p-AKT) levels – substances which we know significantly amplified during psoriasis.[7,18] These properties make this treatment a potentially useful intervention that should be tested in the management of psoriasis.

DISCUSSION

Leukocytes, cytokines, and keratinocyte growth or differentiation abnormalities are involved in psoriatic skin lesions. Psoriasis vulgaris is a T-cell-driven disease, with type I (interferon-γ-producing) T cells predominating in skin lesions.[19,20] A lymphocytic infiltrate in psoriasis plaques consists of a mixture of activated CD4+ and CD8+ T cells; the latter predominate in lesional epidermis and CD4+ cells in the dermis.[21] The therapeutic benefit of immunosuppressive drugs supports the view that activated T cells are pathogenic effectors of psoriasis.[22] Dendritic cells are found in psoriatic skin lesions, producing interleukin-12 and interleukin-23. Cytokine changes in psoriatic lesions consist of elevated levels of interferon-γ, tumor necrosis factor α (TNF-α), numerous interleukins --such as interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-12 (IL-12), interleukin-17 (IL-17), and interleukin-19 (IL-19)— and multiple chemokines –such as Monokine-Induced-by-Gamma (C-X-C motif chemokine ligand 9, MIG/CXCL9), Interferon-γ-induced Protein 10 (C-X-C motif chemokine ligand 10, IP-10/CXCL10), Inducible T-cell-α Chemoattractant (C-X-C motif chemokine ligand 11, I-TAC/CXCL11), and Mcrophage Inflammatory Protein 3α (C-C motif chemokine ligand 20, MIP3a/CCL20). Interleukin-12 p40 mRNA and expression of interferon-γ, inducible nitric oxide synthase, B7-1, and TNF-α are elevated in psoriatic tissue.[20]. A rheumatoid-like pattern has been identified as one of the most common types of psoriatic arthritis. Autoantibodies directed against nuclear antigens, cytokeratins, epidermal keratins, and heat shock proteins have also been reported in psoriatic arthritis.

Hyperbaric oxygen therapy suppresses the proliferation of macrophages and the formation of foam cells in atherosclerotic lesions.[21] hyperbaric oxygen therapy also intensifies the suppressive function of T lymphocytes, normalizes cell-bound immunity, and decreases the serum concentration in immune complexes.[22] The immunosuppressive effects of hyperbaric oxygen therapy include suppression of autoimmune symptoms, decreased production of interleukin-1 and CD4+ cells, and increased percentage and absolute number of CD8+ cells.[17] In addition, long term hyperbaric oxygen therapy exposure suppresses development of autoimmune symptoms such as proteinuria, facial erythema, and lymphadenopathy. hyperbaric oxygen therapy decreases the CD4:CD8 ratio and proliferation of lymphocytes, and activates neutrophils to migrate to regions of high oxygen tension.[23] hyperbaric oxygen therapy suppresses TNF-a production induced by lipopolysaccharide, lipid A, and phytohemagglutinin A.[24] A marked decrease in interleukin-1 and interleukin-2 production, and a significant decrease in prostaglandin E2 production have been observed. The positive clinical effects that hyperbaric oxygen therapy has in the treatment of chronic inflammation may relate to its effects on secretion of interleukin-1, interleukin-6, and TNF-a. The effects of hyperbaric oxygen therapy on prostaglandin, nitric oxide, and cytokines involved in wound pathophysiology and inflammation in particular were recently reviewed.[12] That review indicates that hyperbaric oxygen therapy has important effects on the biology of cytokines and other mediators of inflammation. Hyperbaric oxygen therapy causes downregulation of cytokines and upregulation of growth factors. It transiently suppresses stimulus-induced proinflammatory cytokine production and affects the liberation of TNF-a and endothelins. Vascular endothelial growth factor levels are significantly increased with hyperbaric oxygen therapy therapy, whereas levels of prostaglandin E2 and cyclo-oxygenase-2 mRNA are markedly reduced. Therefore, the anti-inflammatory and immunosuppressive properties of hyperbaric oxygen therapy might account for its efficacy in the cases presented here.

SUMMARY

Considering all the theoretical values, hyperbaric oxygen therapy may have a place in the management of psoriasis. Our literature review, although suggestive, do not yet allow one to conclude that hyperbaric oxygen therapy treatment is significantly beneficial in the treatment of psoriasis. While some preliminary evidence suggested hyperbaric oxygen therapy might have potential advantage for psoriasis, we emphasize that the findings presented here require confirmation by further controlled studies to fully understand the mechanisms underlying these effects, to draw a definitive conclusion may be drawn, and to establish the safety and efficacy of hyperbaric oxygen therapy for this condition.

It is also important to note that hyperbaric oxygen therapy

carries some risks and is not appropriate for everyone, so it should only be used under the guidance of a qualified healthcare professional. However, we hope our review will will provide a basis for elucidating the mechanisms of action, stimulate further investigation of the therapeutic potential of hyperbaric oxygen therapy alone or in combination with other modalities such as phototherapy in psoriasis, and consequently pave the way for further controlled studies which include large numbers of patients and thorough monitoring of cytokines and inflammatory mediators to help us to explore the effect of hyperoxygenation on psoriasis and elucidate its mechanism of action.

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