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REVIEW ARTICLE

Threshold Concept of Pro-inflammatory Markers in Patients with Acne Vulgaris

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ABSTRACT

Acne vulgaris is an inflammatory condition of the pilosebaceous follicles that has no known cause. Hyperplasia of sebaceous glands and increased sebum output, hypercornification of pilosebaceous duct, aberrant colonization, notably by *Propionibacterium acnes*, and inflammation all play a role in the etiology of acne vulgaris. The involvement of oxygen-free radicals and antioxidant enzymes in the aetiopathogenesis of acne vulgaris has been the subject of recent research. When antioxidant enzymes fail to protect cell and organelle membranes from oxidative damage, oxygen-free radicals cause lipid peroxidation.

Oxidative stress affects all biological components by attacking lipids, proteins, and DNA. Among these illnesses, lipid damage caused by oxidative stress-induced lipid peroxidation is particularly significant to acne. The oxidative lipid breakdown in the skin, which is not merely a byproduct of the acne process, was proposed as the chemical etiology of acne. The lipid peroxidation results, lipid peroxides, can be both a cause and an acnegenic agent. This lipid peroxidation notion is supported by a study that shows lipid peroxidation occurs in acne and that site-specific free radical damage and lipid peroxidation products may be involved in the initiation of inflammation. Because the etiology and pathogenesis of acne are poorly known, and no single, major cause has been discovered, this paper was aimed to review the background documents in the scientific literature and focus on the following Question: Which particularly pro-inflammatory substance might derive and consequence of acne? How could be improve the knowledge regarding the potential therapeutic target of Antioxidants in the regulation of oxidative stress of acne patients?

INTRODUCTION

Acne disease is a pilosebaceous duct inflammatory disorder produced by four primary pathophysiologic conditions: androgen-driven sebum production, *Propionibacterium acnes* proliferation, keratinocyte proliferation and desquamation irregularities that contribute to ductal blockage and inflammation.[1]

AGGRESSIVE SKIN AGENT

Biochemical Effect of Oxidative Stress in Acne

The structure of nucleic acids is destroyed when they are exposed to reactive oxygen intermediates such as hydrogen peroxide (H_2O_2), superoxide anion (O^*), and hydroxyl radical (HO^*).

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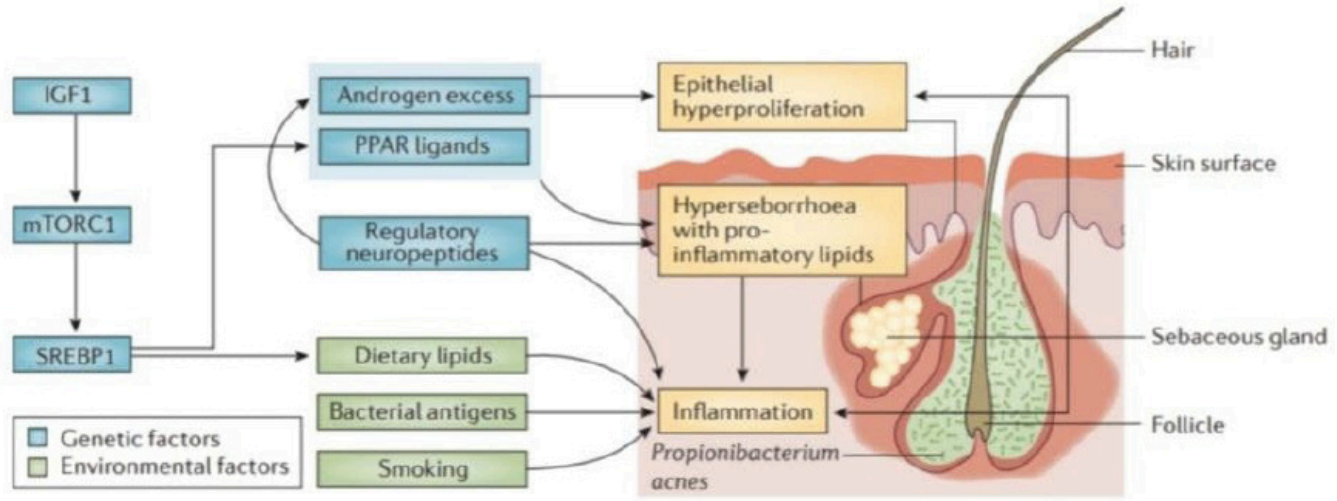

Figure 1: Tangled network of four core events in acne formationhair shaft and sebaceous gland.[2]

Proteins, and cell membranes, result in oxidative stress. Increasing such intermediates causes cumulative harm from ROS, which contributes to a variety of illnesses.[3] An increase in the inflammatory state induced by oxidative stress has been proposed as a key factor in developing and progressing diseases linked to obesity. Furthermore, an increase in inflammatory cytokine levels could contribute to an increase in oxidative stress.[4]

Oxidative Stress and Skin

The equilibrium between oxidants (free radicals) and antioxidants is abnormally skewed in favor of the oxidants in oxidative stress. An imbalance between the production and elimination of reactive oxygen species (ROS) causes cellular damage and disease in the skin. Several biological mechanisms are affected by oxidative stress, including inflammation, signaling cascades, cell metabolism, cellular proliferation, and aging. Increased free radicals can affect the structure and function of proteins, nucleic acids, and lipids and cause tissue damage. During the last two decades, more study has been done on how persistent oxidative stress can cause chronic inflammation, which can eventually lead to chronic diseases like cancer, cardiovascular, neurological, and pulmonary ailments, and diabetes mellitus.[5]

Oxidative Stress and Acne

p53, HIF-1, AP-1, NF-B, PPAR-, Nrf2, and -catenin/Wnt are all transcription factors that can be induced by oxidative stress. There are over 500 genes that code for inflammatory cytokines, chemokines, and anti-inflammatory compounds, growth factors, and cell cycle regulatory molecules that can be activated by these substances.

According to reports, one of the first activities in the acne process is the production of inflammatory substances. Within the pilosebaceous position, The environment is transformed by oxidative stress from one that is unfavorable for anaerobic bacteria colonization to one that is ideal for their colonization. The oxygen level in the follicle is altered by sebum oxidation, creating an excellent environment for *P. acnes* to proliferate. Despite the need for greater research and investigation, oxidative stress and inflammation establish the foundation for all future acne-causing pathogenic agents.[5]

Pro-inflammatory Marker of Acne

Free radicals are formed naturally due to biochemical activity, and the body can keep them in check under normal circumstances. However, if free radical production is high, cells and tissue may be harmed. Free radicals are harmful and destructive agents that are constantly created and can be made from oxygen, causing biological molecules to be affected and damaged. Protein carbonyl, peroxidized lipid products, and DNA partitioning or breaking are the most common indicators of damage.[6]

An organism's antioxidant system is required to protect it against the detrimental effects of these compounds non-enzymatic antioxidants such as vitamin A, as well as antioxidant enzymes (superoxide dismutase, catalase, and glutathione peroxidase) (retinol), glutathione, vitamin E (tocopherol), uric acid, and vitamin C are all involved in this system (ascorbic acid). An oxidative stress situation is caused by an imbalance between free radical generation and antioxidant defense, which may be involved in aging events. There were two sorts of free radical origins: endogenous and external. Endogenous sources include those produced intracellularly and used by the cell and those produced within the cell but discharged into the surrounding environment. Intracellular free radicals are produced by the auto-oxidation and eventual inactivation of molecules such as reduced thiols and flavins. They can also occur as a result of particular lipoxygenases, oxidases, peroxidases, cyclo-oxygenases, and dehydrogenases working efficiently. Paradoxically, electron transfer from metals like iron to oxygen-containing molecules can stimulate free radical activities; antioxidants can also create free radicals. Endogenous free radical molecular species

make up a large percentage of free radical molecular species. Free radicals are produced by ionizing radiation (from the sun, industry, medical X-rays, and cosmic rays), ozone and nitrous oxide (primarily from automobile exhaust), heavy metals (such as mercury, lead, and cadmium), alcohol, cigarette smoke, unsaturated fat, and other chemical compounds and compounds found in water, food, and air. Free radicals created by ionizing radiation have exogenous origins, which play a key role in their creation. Ionizing molecules transport energy into water, causing the water molecule to ionize. Free radicals are formed when the produced water ions dissociate.[6]

Free radicals include both reactive nitrogen species (RNS) and ROS. Nitric oxide ($NO^{\bullet}$) and nitric dioxide (NO_2) are two types of nitric oxide. The reactive nitrogen species in question is peroxynitrite. The reactive oxygen species involved are superoxide anion, hydrogen peroxide (H_2O_2), and hydroxyl radical ($OH^{\bullet}$).[7]

Changes in this redox equilibrium, induced by increased ROS concentrations and/or decreased antioxidant concentrations, produce oxidative stress. Protein oxidation has been linked in a number of studies as a primary source of cellular dysfunction described with aging as well as a variety of other protein structural abnormalities. Inhibition of a wide range of enzyme activity has been described.[8] In acne, sebum produced by the sebaceous glands, content changes, and reactive oxygen species (ROS) may be released from the impacted wounded follicular walls. At the same time, sebum produced by the sebaceous glands, content changes, and ROS may be released from the impacted wounded follicular walls. This is regarded to be the source of the development of inflammation in the disease mechanism. Furthermore, certain acne medications work by reducing ROS.[11] These radicals are generated with the reduction of oxygen to water, as shown in Figure 1.

These radicals are generally created slowly, and the antioxidant enzymes present in the cell work to eliminate them.[9] Figure 2 shows ROS generation and its effects on cellular functions.[10]

Lipid peroxidation is a ROS-involved form of various hazardous lipid aldehydes and lipid hydroperoxides that act as secondary signaling intermediates in the reproduction of oxidative stress signals that have a role in the pathophysiology of human health and illness. According to recent research, lipid aldehydes formed from lipid peroxidation sustain a variety of human clinical issues involving numerous inflammatory disorders. Lipid peroxidation products can cause the production of pro-inflammatory cytokines as well as the stimulation of peroxisome proliferator-activated receptors (PPARs) . PPARs are nuclear transcription factors that play a role in maintaining lipid metabolism as well as controlling the inflammatory response.[12]

Lipid Peroxidation and Acne

Although lipid peroxidation is visible in acne, and localized free radical injury and peroxides may play a role in the harmful inflammatory processes, Other studies have discovered that when sebum components, notably squalene, are present, the damaging inflammatory processes are exacerbated, are oxidized, they promote comedogenicity. Squalene has been shown to be very vulnerable to oxidation, and researchers have revealed that acne patients have much greater quantities of squalene and its oxidized metabolites than healthy people.[13]

Malondialdehyde is an excellent index for measuring the range of the peroxidation process, as the collapse of polyunsaturated fatty acids produces it. The amount of malondialdehyde produced during the peroxidation of microsomal membranes varies depending on the type of tissue, making it difficult to compare the range of lipid peroxidation.

Only unsaturated fatty acids with three or more methylene-intermittent double bonds can finally yield malondialdehyde. Hence diversity in the synthesis of this molecule may be due to lipid structural reflux rather than lipid peroxidation capabilities.[14]

On the other hand, lipoperoxidation affects the proliferation and development of keratinocytes. Furthermore, lipid peroxidation products can activate receptors triggered by peroxisome proliferators, resulting in the PPARs. Nuclear transcription factors, known as PPARs, function in lipid metabolism and inflammation regulation. Surprisingly, enzymes involved in the manufacture of a variety of eicosanoid metabolite products, 5-lipoxygenase (5-LOX), for example, has

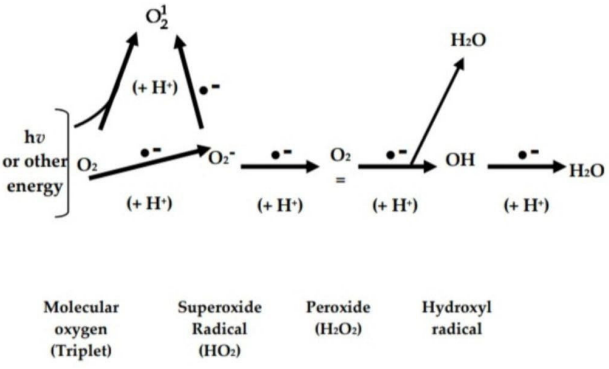

Figure 1: The system of active oxygen. In four single-electron stages, molecular oxygen is reduced to water.[6]

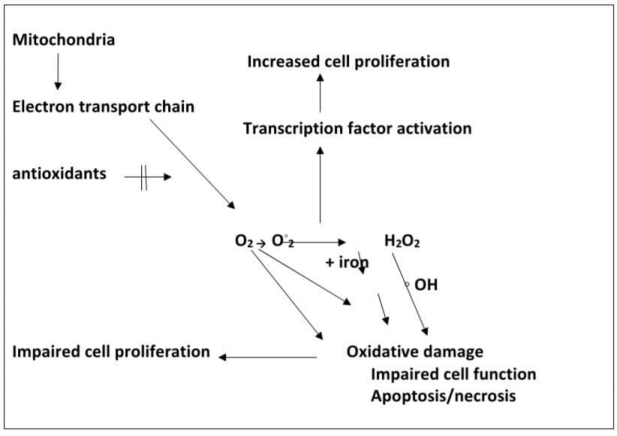

Figure 2: Generation of ROS and its effects on cell function.[10]

been discovered to be expressed at higher levels in acne-prone skin than in healthy skin.[15]

The LOX products have been associated with keratinocyte hyperproliferation, a symptom of inflammatory skin conditions,[16,17] Induced IL-6 and IL-8 expression in human sebocytes.[18] These are only a few of the side effects of 5-LOX activation.[19] Finally, it's critical to expand our understanding of antioxidants' potential therapeutic targets in the regulation of oxidative stress in acne sufferers. This article summarized some of the most recent research on acne's chemical pathology. The information gathered as a result of these efforts will undoubtedly aid in providing a more thorough, integrated view of the entire spectrum of skin disease.

Knowledge Gap

Acne vulgaris is a prevalent skin illness that has a significant influence on one's quality of life. A rising number of epidemiological, medical, demographic, and social studies have lately been published that focus on various contributing factors in the development of acne. Nonetheless, the link between biochemical variables and acne is still being researched.

Acne's etiology and pathophysiology aren't totally understood, and there isn't a single major cause. Observations of several oxidative stress markers have demonstrated that patients with acne are subjected to heightened cutaneous and systemic oxidative stress in numerous research over the last several decades.

This review is part of a case-control study that looked at the effects of specific biochemical markers on acne and created a framework for multidisciplinary research teams to look into the potential correlation between human biomarkers and acne patterns. Acne is most common during adolescence, and it is affected by both age and gender. Acne has also been decreasing in occurrence as people have become older. When it comes to adolescent acne, males outnumbered females, whereas the situation was reversed in terms of post-adolescent acne. In addition, factors including family history, obesity, oily and mixed skin, irregular menstrual cycles, sweet food, fatty food, dairy products, smoking, improper cosmetic use, poor sleep quality, and stress can all have a negative impact on acne. Furthermore, environmental elements such as temperature, sun exposure, air pollution, and different natural environmental factors play an important effect.

As a result, further qualitative and quantitative research is required to assess the impact of most of these factors on acne. This study aims to determine the direct links between previous events and acne to find a solution for such a chronic disease.

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