Role of Oxygen Nanobubbles in Treatment of Acne Vulgaris

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The skin is a major organ, and oxygen benefits the skin as with all organ systems. On an epidermal level, shortage of oxygen affects cellular function and cell division leading to reduced cell turnover and impaired barrier function. On a dermal level, shortage of oxygen impairs fibroblast function which is responsible for collagen and elastin production.

While capillary delivery of oxygen to the dermis is the primary source, a large amount of oxygen passes into the skin from the atmosphere. This fact suggests the possibility of topical oxygen delivery. Multiple modalities for topical application have been attempted, but with limited success. P.T. Pugliese emphasized that, for oxygen to be used as a therapeutic agent, it must first penetrate the skin barrier and then permeate the basal layer (***Pugliese PT; 2008***). Dr. Pugliese states that acne, rosacea, and aging skin will all benefit from topical oxygen therapy. Many scientists and dermatologists agree that topical oxygen delivery can revitalize the epidermis and maintain proper cell turnover (***Bennardo L; 2018***). Additionally, available oxygen kills anaerobic skin bacteria and promotes the healing of skin wounds and irritation (***Stanzl K; 1996***). Ambient supply of oxygen can partially accomplish these tasks (***Stucker M et al; 2002***), but uptake is limited by the known skin barrier function (***Roe DF et al; 2010***). In 2013 researchers from the dermatology department of Mt. Sinai School of Medicine questioned the mechanism of topical oxygen delivery given that currently available products lack evidence of sufficient oxygen penetration for any effective duration (***Straus A; 2013***).

We developed a novel emulsion that delivers oxygen directly to the skin in the form of oxygen nanobubbles and dissolved oxygen in distilled water (O2NBDW) at a concentration in the range of one billion nanobubbles per milliliter. We used a proprietary ceramic nanobubbler (***US Patent US 10,624,841; Lic. Periphex Corp***) and medical grade distilled water to prepare the emulsion. Nanobubbles are invisible unless illuminated by laser light or other imaging methods (Figure 1) (***Filipe V et al; 2010***).

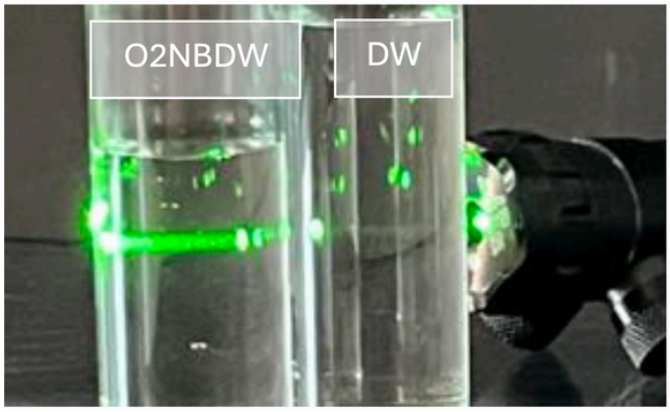

Figure 1: Laser scattering from distilled water vs oxygen nanobubbles in distilled water

Nanobubble technology is widely used in numerous industries including medicine, water purification, wastewater management, and agriculture (***Bravin J; 2023***). The presented emulsion using oxygen nanobubble technology is the first use of oxygen nanobubbles to improve skin health. The nanobubble size (100nm) results in a large gas surface area that amplifies the oxygen effects. The total gas volume within the nanobubbles functions as a gas reservoir for prolonged delivery. Because the nanobubbles are negatively charged, they repel each other making them unable to coalesce into larger, less stable microbubbles. The surface charge and the nanoscopic scale allow the nanobubbles to be neutrally buoyant and stable in the emulsion for months (Figure 2) (***Nirmalkar N et al; 2018***). This stability has been demonstrated both in our laboratory and in other laboratories.

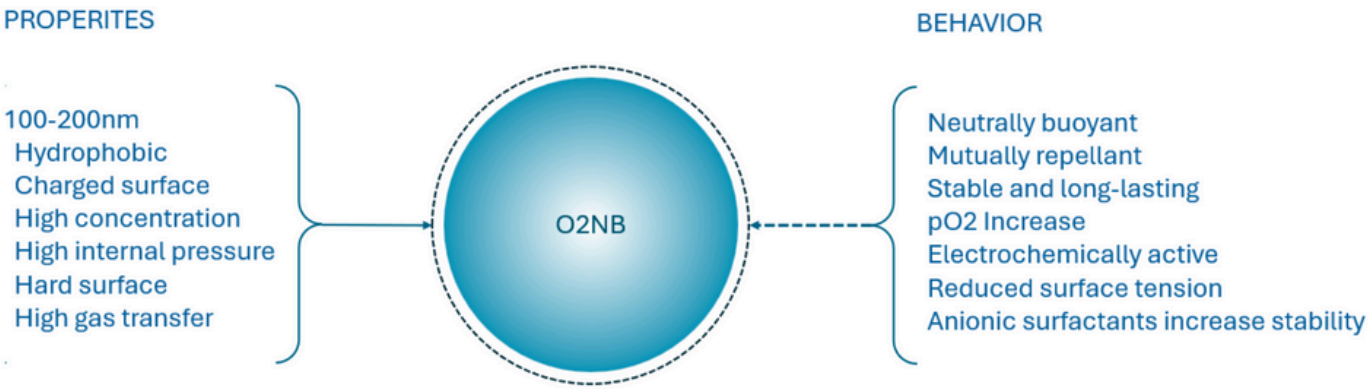

*Figure 2: Properties and resulting behaviors of oxygen nanobubbles (**after Viafara-Garcia 2023**)*

That stability and the oxygen reservoir function of the nanobubbles suggested that the emulsion would work well as a topical treatment. An initial clinical study with the emulsion applied to subjects with acne showed substantial amelioration of acne lesions as well as improved hydration and skin texture. Illustrative cases are shown in Figure 3. In a more recent study, 88% of the 66 subjects showed improvement with almost 40% of this group describing the improvement as dramatic (***http://www.ao2clear.com***).

These studies confirmed our expectations. However, in order to advance the use of the emulsion for skin disorders, we need to understand the role of the oxygen nanobubbles in the pathogenesis of acne.

All cells, skin cells included, require a sufficient supply of oxygen. Insufficient oxygen supply to the cells leads to a state of hypoxia. It is now recognized that a protein, Hypoxia Inducible Factor (HIF1α), is centrally involved in many aspects of homeostasis. HIF1α increases in hypoxic conditions becoming a sensor of the cellular oxygenation status as well as a key regulator of a broad range of cellular and systemic responses to hypoxia (***Owen J et al; 2016***). Additionally, HIF1α plays a regulatory function in response to molecular signals of infection and inflammation occurring in a hypoxic environment.

The situation is particularly pronounced in skin follicles. Sebum is produced in sebaceous glands connected to the follicles. Excessive sebum is considered one of the primary causes of acne. The overproduction of sebum is a direct result of the hypoxic environment. HIF1α plays a critical role in the signaling process that triggers excess sebum production (***Choi K; 2021***). Hypoxia-driven increase in HIF1α upregulates leptin,

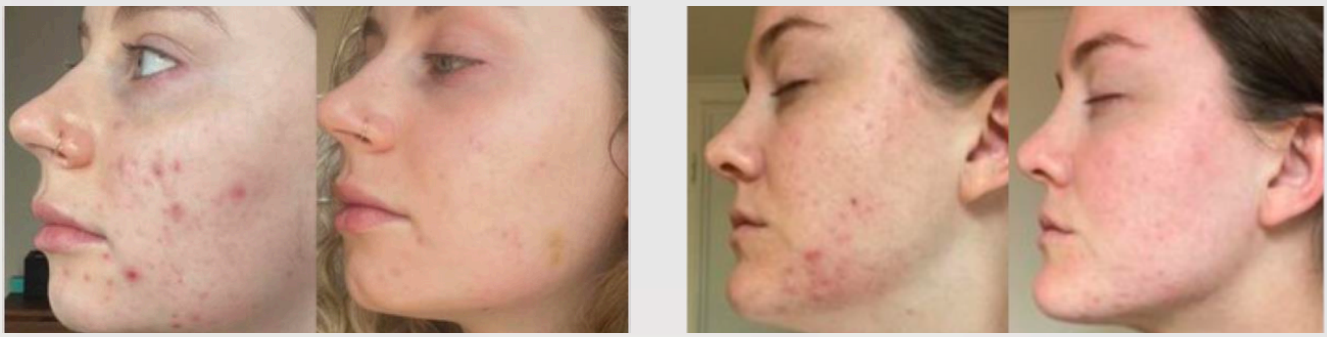

Figure 3: Illustrative cases before and after treatment with O2NBDW. Emulsion was applied twice daily for four weeks using cellulose sponges.

a hormonal mediator of the inflammatory response (***Kellar RW; 2013***). Leptin activates increased sebum production as well as an over-proliferation of keratinocytes (***Danby FW; 2013***). The excess population of keratinocytes combined with the overproduction of sebum creates a keratin plug of the duct of the sebaceous gland which can result in glandular rupture provoking an innate immune response and localized inflammation (***Melnick BC; 2016***). With sufficient oxygen delivery to the skin, HIF1α is maintained at a low value compatible with optimal homeostasis by preventing or reversing hypoxia. This model is outlined in Figure 4.

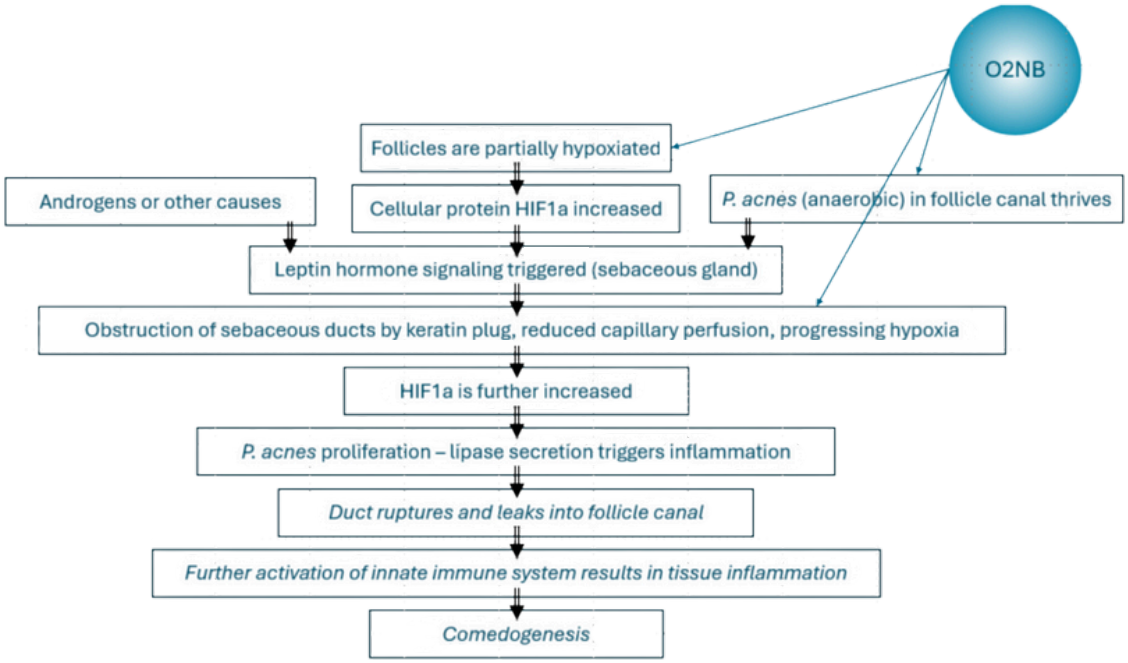

Figure 4: Model of pathogenesis of acne and proposed action points of oxygen nanobubbles

It stands to reason that the novel nanobubble emulsion intervenes with the hypoxic triggers at the top of the entire inflammatory cascade that causes the follicular plugging. With application of the emulsion of oxygen nanobubbles, HIF1α does not increase, leptin is not activated, and sebum overproduction and keratinocyte proliferation do not occur. In addition, oxygen also inhibits the growth of the anaerobic bacteria (*C. acnes*) that play a central role in inflammatory acne providing a parallel mechanism in suppressing acne.

We propose that the unique combined properties of oxygen nanobubbles facilitate their permeation into the skin and follicles which drives the dramatic oxygen gradient between the emulsion and the dermal cells. Penetration of the normal dermal barrier to surface liquids is likely directly at the level of the follicles (***Otberg N et al; 2007***). This allows enhanced oxygen delivery in the form of oxygen nanobubbles and dissolved oxygen at the adnexal structure responsible for acne formation. The stability of the nanobubble reservoir and the high concentration of available molecular oxygen in the emulsion make it a unique and effective formulation for topical oxygen therapies.

That said, this is a *proposed* mechanism. To validate the model, we recommend a battery of four experiments. The first is to demonstrate increased oxygen pressure (pO2) in the skin with application of the emulsion. The second is to show commensurate reduction in follicular hypoxia, perhaps using HIF1α as a marker. The third is to assess all inflammatory markers following application of the emulsion. And the fourth is to do quantitative measurements of the presence of *C. acnes*. We are excited to move forward with these proposed experiments.

FINANCIAL DISCLOSURES

Some of the research presented here was supported by O2 Partners and Periphex Corporation in Austin, Texas. Valerie Hanft, MD, serves as an advisor and has equity ownership in O2 Partners. Zvi Yaniv, PhD, serves as an advisor and has equity ownership in Periphex Corporation. Royce Johnson, PhD, has no financial relationships related to this research.

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