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THE POTENTIAL OF TOCOTRIENOLS TO MITIGATE THE EFFECTS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE: A REVIEW

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Introduction

Chronic Obstructive Pulmonary Disease (COPD) is characterized by an irreversible and persistent airflow limitation over time.[1] Clinical manifestations include chronic bronchitis and emphysema, occurring with dyspnea, chronic cough, and sputum production, among other symptoms. Symptom occurrence and severity varies between individuals. This incurable and chronic condition takes an incredible toll on human life. The Global Burden of Disease lists COPD as the third leading cause of death worldwide, something the World Health Organization did not predict to occur until 2030.[2,3] Additionally, COPD is the third leading cause of disease-related death in the U.S. In 2015, more than 6% of American adults aged 40 years or older reported a COPD diagnosis.[4] Currently, there is no cure for COPD. At present, recommendations and treatments include smoking cessation and avoidance of air pollutants and pharmacological interventions to prevent and treat disease exacerbations.[1] The clinical and economic burden of the more than 380 million worldwide cases leads researchers to search for alternative means of prevention and safe and cost-effective treatments.

Inhalation of combustible tobacco products is the single most causal factor for developing COPD. Indeed, the 2014 U.S. Surgeon General Report concluded that approximately 80% of cases resulted from cigarette use.[5] However, smoking is not the only cause. In an official statement from the American Thoracic Society, Eisner et al. systematically examined all relevant research and concluded that numerous factors contribute to the onset of the respiratory burden indicative of COPD.[6] For example, there is suggestive evidence that genetics plays a role. Cutis laxa and α_1-antitrypsin deficiency are two known inherited disorders that contribute to non-smokers' and smokers' contraction. Additionally, there is sufficient evidence to suggest a causal relationship between occupational agent exposure and COPD.

Furthermore, for women, the burning of biomass fuels used for home-cooking is a significant contributor in low-and-middle-income countries, in particular.[6] Lastly, there is also limited but suggestive evidence proposing that poor nutrition contributes to COPD development, as antioxidants play a vital role in neutralizing damaging free radicals. No matter the cause, treatments typically do not differ.[6] The following review of the literature aims to explain the complex pathophysiology of COPD, detail the roles of inflammation and oxidative stress induced by the noxious particles previously mentioned and suggest a potential role of the vitamin E isoforms, specifically tocotrienols, in serving as a complementary therapy.

Literature Review

I. Pathophysiology of COPD

A. *Pathogenesis and Clinical Presentation*

While smoking history is considered a major risk factor, growth and development may impact COPD risk as much.[1,7] For example, a meta-analysis of data from the British Women's Heart and Health Study found that low birth weight was associated with a premature decline in lung function in adulthood, measured with spirometry as forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC).[7] Another study evaluating data from three longitudinal cohort studies found that a substantial proportion of COPD sufferers did not experience an accelerated decline in FEV_1 from normal levels but instead had low levels since childhood.[8] Throughout life, exposure to environmental pollutants (e.g., smoke from cigarettes and biomass fuel) continues to cause deleterious effects to lung tissue through oxidative and inflammatory damage, altering their structure and impeding proper functioning.

Chronic bronchitis, emphysema, and small airway fibrosis occur as a result of this destruction. Chronic bronchitis is defined as a chronic productive cough lasting for more than three months in a period of two years and is thought to result from goblet cell hyperplasia resulting in mucus hypersecretion.[9–11] In this disorder, bronchiole tubes in the lung become inflamed, impeding airflow to the alveoli or gas exchange sites. In emphysema, usually a later onset, the alveoli lose their elasticity, hindering carbon dioxide (CO_2) and oxygen (O_2) interchange, resulting in patient dyspnea.[11,12] More recent research investigating COPD's progression has found that small airway fibrosis may play a more critical role in disease development than initially thought.

COPD is not generally thought of as a fibrotic disease.[11] It is commonly regarded as chronic inflammation of the bronchioles, small airway narrowing, and alveolar damage as described above. However, more recent investigations into fibrotic lung diseases revealed that pulmonary fibrosis appears to be a central mechanism in small airway narrowing, a significant driver of COPD progression.[11] It is believed that reactive oxygen species (ROS) in cigarette smoke results in fibroblasts' apoptosis,[13] increasing senescence,[14] and initiating fibrosis . One potential mechanism for this fibrosis involves increased expression of transforming growth factor β_1 (TGF-β_1) observed in people with COPD. This chemokine may play a primary role in macrophage recruitment and epithelial dedifferentiation into mesenchymal cells that release fibronectin contributing to fibrosis in peribronchial spaces.[15,16]

B. Oxidative Stress and Inflammation

It is a well-documented phenomenon that oxidative stress is a primary driver in the development of COPD. The lungs are especially susceptible to damaging oxidants given their role in gas exchange, mitochondrial respiration, and inflammatory reactions to pathogenic infections.[17]

In healthy lungs, numerous antioxidant defense strategies neutralize these free radicals. Reduced glutathione (GSH) plays a significant role, along with vitamin C, vitamin E, and uric acid found in the epithelial lining fluid of the lungs.[17] However, free radicals present in cigarette smoke and other pollutants overwhelm these internal defenses resulting in oxidative damage and inflammation that drive COPD's progression.

Cigarette smoke, in particular, is derived from nearly 5,000 chemicals, many of which are oxidants.[18] In fact, cigarette smoke contains more than 10^{14} oxidants per puff. Many of these oxidants are long-lived semiquinones found in the tar phase. Due to the Fenton reaction, semiquinones produce damaging hydroxide radicals ($^{\bullet}OH$) and hydrogen peroxide (H_2O_2).[19] Similarly, recent investigations into electronic (e)-cigarette vapor have found anywhere between 2.5×10^{13} and 10.3×10^{13} radicals per puff, demonstrating a probable likelihood that the supposedly safer e-cigarettes also contribute to COPD development.[20] In healthy lungs, synthesis of GSH is upregulated in the presence of oxidative stress;[21] however, in smokers and people with COPD, downregulation of nuclear erythroid-2-related-factor-2 (Nrf2), a primary antioxidant transcription factor, leads to decreased levels of GSH and antioxidants in the epithelium and alveolar macrophages.[22]

ROS production also instigates inflammation through the stimulation and recruitment of many inflammatory cell types. The activation of lung epithelial cells and resident macrophages recruit and activate neutrophils, eosinophils, monocytes, and lymphocytes, pushing further ROS damage in response to their inflammatory intermediaries.[23] Initially, macrophages' role is to engulf the pollutant entering the cell, reducing their deleterious effects. However, with increased exposure, the acute inflammation meant to heal the epithelium turns chronic, modifying the individual's response. Furthermore, the activation of these white blood cells (WBC) generates

superoxide anions ($O_2^{\bullet-}$), which are converted to H_2O_2 by superoxide dismutase (SOD), and additional $^{\bullet}OH$ is formed by way of the Fenton reaction.[24]

Furthermore, these WBC release pro-inflammatory cytokines, chemokines, and interleukins, impairing barrier function and allowing for bacterial penetration and COPD exacerbations. Endogenous ROS and reactive nitrogen species (RNS) form in myriad ways, further contributing to the system's oxidant/antioxidant imbalance. Increases in ROS and RNS in smokers also contribute to the nitration and oxidation of plasma proteins, increasing lipid peroxidation and protein carbonyl formation, pushing COPD's inflammatory response.[23] Moreover, ROS drives inflammation through the activation of plasma membrane receptors, mitogen-activated protein kinase (MAPK) and protein kinase C (PKC), and transcription factors, primarily the nuclear factor κB (NFκB) pathway.[23]

People with COPD experience recurrent disease exacerbations marked by increases in inflammatory cells and their mediators into the lungs. A detailed look into these inflammatory pathways is necessary to investigate potential alternative treatments. Inflammatory mediators like interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) activate inhibitor of nuclear factor κB kinase, thus phosphorylating NFκB.[25] The phosphorylated NFκB heterodimer translocates to the nucleus, binding to specific inflammatory gene receptors, thereby promoting their transcription. These inflammatory genes promote the transcription of additional pro-inflammatory mediators (e.g., IL-1β, IL-6, IL-8) in a feedforward response, driving disease progression. C-reactive protein (CRP), IL-6, IL-8, and TNF-α are markers of disease severity in COPD.[26] IL-6 serves as the chemical messenger that activates CRP and is a marker of inflammation.[27] Produced by macrophages and found in the sputum of COPD patients, IL-8 recruits neutrophils, B cells, and T cells to the lungs, increasing the inflammatory response.[28,29] TNF-α, an activator of NFκB, is

found in higher amounts in the sputum during COPD exacerbations; however, this is not a reliable marker for COPD as it is inherently elevated in most smokers.[27]

These chemokines and the ROS produced in cigarette smoke and other pollutants are the primary drivers of COPD and its progression and persist even after smoking cessation.[17] Results of these inflammatory processes include alveolar septal cell death (apoptosis), recycling of cell components (autophagy), and cellular necrosis, reducing the alveolar cell surface area and causing emphysema.[30] Additionally, this accumulation of ROS activates TGF-β which stimulates small airway fibroblasts to produce collagens contributing to small airway fibrosis.[11] Nevertheless, current treatments are lacking to ameliorate these root causes of COPD.

C. Current Treatments

At this time, the most prevalent treatments for COPD are inhaled corticosteroids (ICS), long-acting muscarinic antagonists (LAMA), and long-acting β_2-agonists (LAβA). However, these treatments do nothing to remedy the oxidative stress indicative of COPD development and progression and do very little to treat the inflammation described above. Glucocorticoids primarily exert their influence by switching off the inflammatory genes responsible for transcribing the mediators of inflammation described above.[25] These steroids bind to specific glucocorticoid receptors mitigating the effects of NFκB. Glucocorticoids also work by inhibiting the stabilization of specific mRNAs that are resistant to degradation in inflammatory conditions. While these drugs work well to decrease inflammation in asthma, they are much less effective in COPD.[17] Numerous factors contribute to the inflammatory conditions observed in COPD, including redox signaling of pro-inflammatory kinases (e.g., MAPK, PKC) and transcription factors (e.g., NFκB), as mentioned previously. Additionally, mucus hypersecretion by goblet cells, extracellular matrix remodeling,

autophagy/apoptosis, epigenetic changes (e.g., hypermethylation), cellular senescence/aging, and endothelial dysfunction all play a role.[31] Given these multifactorial causes and since only about 10% of COPD patients respond favorably to corticosteroids, other therapies are usually considered first.

LAβA and LAMAs are usually the first-line defenses used to treat COPD. They are used as either monotherapy or in some combination.[1] Nannini et al. showed that in patients with moderate to severe COPD, an ICS combined with a LAβA was more effective at improving lung function and reducing COPD exacerbations versus either drug on its own.[32,33] Alternative therapeutics include phosphodiesterase-4 (PDE4) inhibitors, mucoregulators, and antibiotics, and others.[1] While these medications may provide some therapeutic benefit, they are not without side effects. For instance, LAβA may increase cardiac arrhythmias in some patients and result in hypokalemia in thiazide diuretic patients.[1,34] ICS use is strongly associated with a higher prevalence of several unfortunate side effects, including pneumonia, and some studies suggest that long-term use may lead to low bone mineral density, cataracts, and bacterial infections.[35–38] Moreover, anti-inflammatory medications such as PDE4 inhibitors show even more adverse effects than the inhaled drugs previously reviewed. Common side effects include diarrhea, nausea, reduced appetite, weight loss, and insomnia.[39] Prolonged antibiotic use may reduce exacerbation frequency in some patients; however, this inevitably causes bacterial resistance and even impaired hearing.[40,41] Given that these drugs do not slow COPD progression and come with numerous harmful side effects, investigations into other treatment modalities are warranted.

II. Therapeutic Potential of Vitamin E

A. Isomers of Vitamin E

ROS-stimulated inflammation through recruitment of inflammatory cytokines and activation of the NFκB pathway, paired with ineffective treatments and oxidant/antioxidant imbalances in patients with COPD, warrants investigation into nutraceutical adjunct therapies. Naturally occurring vitamin E compounds may provide a unique answer given their combined antioxidant and anti-inflammatory effects.[42] A 2016 study investigating the antioxidant potential of vitamin E (α-tocopherol) showed reduced oxidative stress markers in smokers during a 36-month supplementation trial.[43] Another 20-year prospective study showed vitamin E and fruit intake were associated with a reduced COPD mortality rate.[44] Interestingly, no effect was observed for vitamin C, β-carotene, vegetable, and fish intake in the same study. Other epidemiolocal studies have found similar results concerning a reduced risk of inflammatory cardiovascular diseases associated with vitamin E intake, while vitamin C and β-carotene do not appear to diminish risk.[45]

However, not all vitamin E isoforms are equal. In 1922, α-tocopherol was the first analog of the fat-soluble vitamin E to be isolated. Subsequently, seven other forms were discovered, and so, there are eight distinct vitamers.[42] These eight isoforms can be organized into two distinct subgroups: tocopherols (T) and tocotrienols (T3). Both subgroups contain a chromanol ring with a 16-carbon side chain. The tocopherols' side chain is saturated with hydrogens, whereas tocotrienols, as the name suggests, contain three unsaturated double bonds. Each subgroup contains four isoforms (α, β, γ, and δ) and differ only in the number and placement of methyl groups on their chromanol ring.[42]

Furthermore, T and T3 differ in their sources. Tocopherols are the more abundant form found in all photosynthetic organisms, including fruits, leafy greens, nuts, and seeds.[46] Of note,

their primary role in plants appears to be neutralization of photosynthetic-derived ROS. However, tocotrienols are found only in a small subsample of plants and usually in the non-photosynthetic portion, like the seed. The most abundant sources of tocotrienols in the food supply are rice bran, palm, and annatto oils, with respective T: T3 ratios of 50:50, 25:75, and 10:90.[46] Several studies have looked into the tocotrienol levels in the food supply, and average daily consumption is only a few milligrams (mg), much lower than the amounts studied for health benefits.[46,47] Researchers have investigated the antioxidant and anti-inflammatory properties of vitamin E for many years, although until the 1990s, the vast majority of published research probed α-T, for many reasons.

α-T is the predominant form of vitamin E in the body, and initially, this form was thought to be the most potent antioxidant. However, research on its safety as a supplement is controversial. In the 1994 Alpha-Tocopherol Beta Carotene Cancer Prevention (ATBC) study, α-T was supplemented in over 14,000 male smokers aged 50-69 years for five to eight years.[48] The researchers observed no reductions in lung cancer incidence and were surprised to see deaths from hemorrhagic stroke increased in this group.[48] In another 1996 study probing whether α-T supplementation could mitigate the risks of LDL oxidation, researchers from the Cambridge Heart Antioxidant Study (CHAOS) did observe reductions in non-fatal myocardial infarctions after one year in α-T supplemented participants.[49] However, they also observed slightly higher total mortality rates, albeit without statistical significance, and concluded that future studies should investigate this phenomenon. These findings remain contentious among researchers, and hypotheses on these observations abound.[46] Still, tocotrienols were not used in these studies, and more recent research has suggested that tocotrienols are the more potent antioxidant and anti-inflammatory of the two forms.

All vitamin E isoforms are considered potent antioxidants due to the electron-donating powers of their chromanol ring.[50] Additionally, vitamin E's incorporation into the lipid bilayer offers unique placement to scavenge free radicals and prevent lipid peroxidation. However, several findings suggest that tocotrienols have a greater capacity to scavenge free radicals.[51] In a cell culture study conducted by Serbinova and colleagues comparing the antioxidant activity of α-T to α-T3, tocotrienol's peroxyl scavenging activity was 1.5-fold higher in liposomes than the tocopherol's.[52] Additionally, proton NMR and fluorescence imaging revealed α-T3 was more evenly distributed in the lipid bilayer and had superior maneuverability. The researchers also noted α-T3 was more efficient at chromanoxyl recycling, contributing to its advantage. Notably, γ- and δ-T3 are thought to be the more potent of the tocotrienols.[53] Besides their anti-inflammatory and antioxidant superiority, numerous animal and cell culture studies have shown they are also more cardioprotective and have greater anti-cancer activity and cholesterol-lowering benefits.[54,55] These properties have inspired continuing research into tocotrienols and chronic diseases in cell culture and animal models.

B. Antioxidant and Anti-inflammatory Effects of Tocotrienols

α-Tocotrienol was the first form of T3 to be extensively studied due to its similarity to α-tocopherol.[52] More data from the Serbinova and colleagues cell-culture study revealed that α-T3 had 40-60 times higher antioxidant activity against lipid peroxidation in rat liver microsomal membranes and protected against cytochrome P-450 at a 6.5 times greater rate than α-T against oxidative damage.[52] In another study using human lung carcinoma cells, α-T3 reduced lipopolysaccharide (LPS)-induced cell death and reduced production of TNF-α, IL-6, and IL-8.[56] In human adipose-derived stem cells, Zhao and colleagues demonstrated α-T3's effectiveness in

reducing LPS-induced pro-inflammatory gene expression and thus IL-6 and IL-8 production.[57] Despite these positive results, more extensive research has discovered that γ- and δ-tocotrienols are more powerful antioxidants and have a more significant anti-inflammatory potential than even α-T3.[58] This potency is thought to be the result of these vitamers having an unsubstituted 5-position on their chromanol rings.[46] This region may trap RNS and ROS more effectively, thereby reducing their destructive potential.[45]

γ-Tocotrienol, in particular, is abundant in palm fruit and is a common substituent of tocotrienol-rich-fraction (TRF), a compound derived from palm containing 25% tocopherols and 75% tocotrienols and often used in anti-inflammatory intervention models.[46,59] γ-Tocotrienol appears to have a direct influence on the NFκB pathway. In one study explicitly investigating this pathway in various cell types (e.g., epithelial H1299, A293, and MCF-7 cells, and SCC4 and KBM-5 tumor cells) γ-T3 completely blocked NFκB activation induced by TNF-α, cigarette smoke condensate, LPS, and other cytokines.[60] In another study, Wang and Jiang showed that γ-T3 inhibited LPS-induced NFκB activation and IL-6 production in murine RAW 267.4 macrophages.[61] Furthermore, in 2015, Wang et al. elegantly demonstrated the mechanism of NFκB inhibition, noting that γ-T3 upregulated A20, an inhibitor of NFκB, through modulation of sphingolipids.[62]

Another constituent of palm oil, rice bran, and annatto fruit is the vitamer δ-tocotrienol. In murine RAW and iJ774 macrophages, δ-T3, the primary isoform in annatto oil, was exceptional in reducing inflammasome activation and IL-1β production through inhibition of NFκB and reduced ROS production.[63] In these cells, Buckner et al. induced inflammation by priming them with LPS followed by nigericin and pretreated them with either 1 μM, 2.5 μM, or 5 μM of δ-T3. IL-1β production was reduced in a dose-dependent manner by 30%, 75%, and 80%, respectively,

compared to the control sample. Additionally, fluorescence imaging revealed ROS-production was significantly reduced when treated with δ-T3 compared to the control. The dual antioxidant, anti-inflammatory effects of δ-T3 can be seen in various cell types. In human umbilical vein endothelial cells incubated with LPS, δ-T3 attenuated production of the inflammatory cytokine IL-6.[64] Additionally, δ-T3 inhibited the NFκB pathway and enhanced endothelial nitric oxide synthase (eNOS) activity, an essential enzyme for vascular health as it produces the potent vasodilator nitric oxide (NO). In TNF-α-treated human adipocytes, δ-T3 reduced IL-6 and MCP-1 release.[65] This collection of *in vitro* studies shows that tocotrienols can ameliorate COPD's instigators, including cigarette smoke-induced ROS production and activation of the NFκB pathway. Moreover, when given in pharmaceutical doses (i.e., 800-3200 mg/day) and subsequent incorporation into the lipid bilayer of the body's cells, T3 may be capable of targeting the root causes of COPD progression and not just its symptoms.

Studies from the following animal models show similar *in vivo* results for tocotrienols, and again, highlight the potency of the γ- and δ-T3 isoforms in models of various inflammatory conditions. Like COPD, obesity is an inflammatory condition prone to macrophage recruitment and chemokine production. By comparing mice fed a high-fat diet, a high-fat diet with δ-T3, a high-fat diet with metformin, and a low-fat diet, Allen and colleagues showed that δ-T3 reduced macrophage recruitment and hyperplasia of adipocytes compared to metformin. In 2015, Zhao and colleagues demonstrated that mice fed a high-fat diet supplemented with γ-T3 had lower obesity rates and less insulin resistance to mice fed a high-fat diet solely. In addition, the intervention group exhibited decreased plasma levels of fasting glucose, insulin, and pro-inflammatory cytokines, improved glucose tolerance, and enhanced insulin signaling in adipose tissue.[66] In a house dust-mite-induced asthma model, mice treated with either prednisolone, α-T, γ-T3, or δ-T3

were tested for inflammatory cell counts, cytokine levels, ROS/RNS, and oxidative damage biomarkers.[67] Researchers observed the γ-T3 vitamer to be most efficient in reducing these biomarkers by inhibiting NFκB and enhancing redox-sensitive Nrf2 activity.

In another mouse study, all three tocotrienol isoforms proved effective at modulating the inflammasome when compared to α-T. Qureshi et al. injected mice with varying doses (2.5, 5.0, and 10.0 μg/ kg body weight) of α-T, α-T3, γ-T3, or δ-T3. After one hour, they induced inflammation using a single intraperitoneal injection of pure LPS. While α-T did not significantly reduce serum TNF-α levels compared to the control group, all T3 vitamers significantly reduced inflammation in a dose-dependent manner. δ-T3 outperformed α- and γ-T3 in reducing serum TNF-α levels, with the 10 μg/kg dose providing a 48% reduction.[68] The researchers also observed reduced gene expression of inflammatory cytokines (e.g., TNF-α, IL-1β, IL-6) and inducible NOS, which exponentially increases NO production and contributes to inflammation, with low-dose (<20 μM) injections of the δ-T3 isoform.

Very little research has been conducted on tocotrienols as a treatment for COPD. However, Peh et al. built on their previous work, showing the efficacy of using tocotrienol in a mouse model of COPD.[31] The researchers performed two smoking trials, an 11-day acute model and a 54-day chronic model, in which they exposed BALB/c mice to nine cigarettes per day, five days a week, to induce emphysema-like symptoms. On days 9-11 of the acute model, the mice were treated with either prednisolone (10 mg/kg body weight) or varying doses of γ-T3 (30, 100, 250 mg/kg body weight). Similarly, the mice in the chronic model were treated with either prednisolone (10 mg/kg body weight) or γ-T3 (250 mg/kg body weight) on day 38 and day 53. Both models showed that γ-T3 was more effective than prednisolone at reducing neutrophil counts, cytokine levels, and oxidative damage biomarkers.[31] Additionally, γ-T3 prevented lung function decline and improved

overall lung function. As mentioned, COPD is a chronic, progressive condition with few effective treatments and none to halt its advancement. These promising results indicate γ-T3, or another of the T3 vitamers, could fill that void, mainly through neutralization of free radicals and inhibition of the NFκB pathway.

Conclusion

COPD is a highly preventable condition that is devastating to global health. Its pathophysiology includes oxidative damage, fed by free radicals in cigarette smoke and other noxious particles, which drives inflammation by activating the NFκB pathway. The resulting destruction causes small airway fibrosis, followed by chronic bronchitis and emphysema, leading to debilitating symptoms and poor quality of life. Current therapeutics lack efficacy and safety, leading researchers to search for alternative means of prevention and treatment.

Tocotrienols are a group of powerful antioxidants and anti-inflammatory agents found naturally in the seeds of various plants. While amounts of tocotrienols consumed in foods are only a few milligrams per day, compounds isolated from these seeds could be an excellent adjunctive therapy in nutraceutical form in people with COPD or those at high risk. To test the safety of one of these compounds and whether supplementation could markedly increase bioactive levels, Mahipal and colleagues supplemented 36 healthy subjects with oral doses of up to 3200 mg of δ-T3 daily for 14 consecutive days and observed no adverse events.[69] Additionally, increased plasma levels were observed in a dose-dependent manner, indicating their safety and warranting future clinical studies.

Furthermore, their versatility and safety have been reported in numerous chronic conditions marked by inflammation. Previous research has revealed their anti-cancer, cardioprotective, and

cholesterol-lowering benefits, among others. Indeed, tocotrienols were more effective than prednisolone in a COPD mice model, suggesting their benefit over the currently prescribed treatment regimen. Again, these observations warrant further research into tocotrienols. One or more of these compounds could be safer and potentially more effective at curbing the effects of COPD than the currently lacking treatments. Future research should answer whether dual-therapy LAMA/ICS alone or in conjunction with supplementation of varying milligram strengths of the T3 vitamers is more effective at improving quality of life, reducing disease exacerbations, and delaying the progression of COPD. Additionally, these studies should measure inflammatory cell counts, cytokine levels, ROS/RNS, and oxidative damage biomarkers to determine if T3 effectively suppresses the affected inflammatory pathways and corrects the oxidant/antioxidant imbalances in these patients.

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