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REVIEW

Dietary Approach for Post-COVID Treatment of Olfactory Loss

Shreyashish Roy-Chowdhury [a], Arvindsai Satishkumar [b], Syed Hamza Ahmed [c] Austin A. Mardon [d]
[a] Schulich School of Medicine and Dentistry, Western University, Canada ; [b] Faculty of Science, Western University, Canada ; [c] Faculty of Health Sciences, Western University, Canada ; [d] Adjunct Professor, Faculty of Medicine & Dentistry, University of Alberta, Canada

ABSTRACT
The spread of severe acute respiratory syndrome coronavirus [SARS-CoV-2] has consequently led to the global COVID-19 pandemic. Many patients, whether hospitalized or not, have reported a variety of complications that persist after recovery. The admission for COVID-19 has been associated with anosmia and hyposmia, the inability or decreased ability to smell. Deficiencies in the ability to smell tend to recover within weeks. However, a significant number of cases have been reported in which smell distortions last for several months. Experimental research has identified inflammation as a factor disrupting olfactory neurons. Precisely, local inflammation through cytokine release in sustentacular and horizontal basal cells interferes with the function of olfactory neurons. Further studies have reported that these local inflammatory events are not responsive to common corticoid treatments. Therefore, in order to mediate the recovery of olfaction in COVID-19 patients after viral recovery, this study evaluates vitamin C, vitamin D, vitamin E, and omega-3 polyunsaturated fatty acids to develop a prospective dietary approach with anti-inflammatory properties to reduce the local inflammation of sustentacular and horizontal basal cells.

KEYWORDS: COVID-19; Olfaction; Inflammation; Vitamins; Omega-3 Fatty Acids.

Correspondence: Shreyashish Roy-Chowdhury, Schulich School of Medicine and Dentistry, Western University, Ontario, Canada. Email: sroycho3@uwo.ca

INTRODUCTION

On March 11, 2020, the World Health Organization (WHO) declared the outbreak of the severe acute respiratory syndrome coronavirus [SARS-CoV-2] as a global COVID-19 pandemic. As of January 30, 2021, John Hopkins University has reported over 100 million cases worldwide [1].

The contraction of SARS-CoV-2 is most commonly characterized by fever, dry cough, and tiredness [2]. Many studies have also reported complications in olfaction as a symptom of this virus. A retrospective review across 169 COVID-19 patients by Yan et al. [3] reported outpatient care to be strongly and independently associated with anosmia (the complete loss of smell). Agyeman et al. [4] further reported 41% of 8438 COVID-19 positive individuals experienced olfactory dysfunction. For the majority of individuals who experience distortions in olfaction, they tend to recover this sense within a month [5]. However, there is a growing body of evidence suggesting that the sense of smell can be impaired for longer periods of time after infection. Postviral olfactory complications have been implicated in 40% of adult anosmia cases; COVID-19 accounting for 10-15% of cases [4]. In a six-month follow-up self-report study, Hopkins et al. [6] reported a prevalence of parosmia (distortions of the sense of smell) across 43.1% of their 177 patients with a median interval of 2.5 months (range 0-6). Their study further highlighted 12 patients who reported complete loss of smell.

The mechanism behind olfactory dysfunction is currently known to occur in sustentacular and horizontal basal cells, which are found in the olfactory epithelium [7]. In a study by Brann et al. [8], single-cell RNA sequencing gene expression analysis of human nasal biopsy samples showed the expression of angiotensin-converting enzyme 2 (ACE2) receptors and cell surface transmembrane serine protease 2 (TMPRSS2) in sustentacular and horizontal basal cells. These two proteins serve as critical viral entry points. These observations were matched in a mouse model, where deeper olfactory bulb tissue could be examined. Interestingly, ACE2 receptors were found in vascular cells, predominantly pericytes, and immune cells of the macrophage/monocyte lineage [8]. SARS-

CoV-2 infection to these supporting cells can interfere with neuronal signaling through local inflammation induced by cytokine release. Torabi et al. [9] used Enzyme-linked Immunosorbent Assays (ELISA) to detect levels of proinflammatory tumour necrosis factor α (TNF-α) and interleukin-1-beta (IL-1β) in biopsies of olfactory epithelium from patients with confirmed COVID-19 as well as uninfected controls. They observed significantly increased levels of the proinflammatory TNF-α in the olfactory epithelium of the COVID-19 group compared to the control group ($P<0.05$). Their results ultimately suggest that direct inflammation of the olfactory epithelium could play a role in the loss of olfaction as seen in COVID-19 positive individuals [9].

Inflammation in the nasal cavities is a common factor that leads to anosmia [10]. Common treatments include corticosteroids which serve as effective anti-inflammatory therapy [11]. They are found in the form of nasal sprays which can be purchased with a prescription. Corticosteroids are recognized to suppress the multiple inflammatory genes by reversing histone acetylation activated inflammatory genes. They bind liganded glucocorticoid receptors to coactivators and recruitment of histone deacetylase-2 to the activated transcription complex [11]. However, Trotier et al. [12] reported that olfactory inflammation, in COVID-19 positive individuals, was not responsive to corticoid treatments.

Olfaction is an essential sensory mechanism required for the development of perception. A study done by Pence et al [13] observed that when compared to people without smell loss, people with anosmia had double the chance of experiencing a hazardous event including eating spoilt food. Olfaction is further linked to the well-being of people. Odors are found to influence mood, produce alertness and relaxation, and evoke powerful experiences of pleasure [14]. Further studies have associated a reduction in psychological well-being with the loss of smell [15, 16].

Various supplements consumed through diet have been recognized to reduce inflammation within the body. Their modulatory involvement in the synthesis of proinflammatory cytokines has been therapeutically used to control the pathogenesis of many diseases [17, 18]. In fact, studies have identified an association between nutrient deficiencies and increased inflammatory cytokine levels [19, 20]. Therefore, this review will focus on dietary supplements that have the potential to reduce inflammation induced by cytokines in the olfactory epithelium of post-COVID-19 affected individuals to accelerate their recovery of olfaction. Precisely, this review will target dietary supplements that regulate the production and activity of TNF-α due to its increased levels in biopsies of olfactory epithelium in post-COVID-19 positive individuals [9].

DIETARY APPROACH TO TREATING OLFACTORY LOSS

Vitamin C and E

Vitamin C (ascorbic acid) and vitamin E (α-tocopherol) are both essential antioxidant vitamins for biological functioning [21]. Along with their function in regulating the levels of free radicals in the human body, both vitamin C and E have been implicated in reducing inflammation [22]. A study done by Chen et al. [23] observed vitamin C to significantly decrease the levels of TNF-α in patients with community-acquired pneumonia. Mrityujaya et al. [24] reported similar findings stating that vitamin C decreases proinflammatory cytokines, TNF-α, and innate interferon-γ (IFN-γ). These findings are further supported by the conclusions in a study by Ellulu et al. [25], where supplementation of vitamin C significantly treated and reduced the inflammation, as measured by high-sensitivity C-reactive protein (hs-CRP) and interleukin 6 (IL-6), in hypertensive and/or diabetic adults. Moreover, vitamin E has been stated to also reduce inflammation through suppression of TNF-α. Hashemi et al. [26] associated vitamin E intake with downregulation of gene expression for TNF-α in women with implantation failure. In a study using participants with Metabolic Syndrome, Devarj et al. [27] identified a significant decrease in TNF-α after α-tocopherol supplementation.

Overall, previous literature has identified vitamin C and E as significant regulators of inflammation, particularly through the modulation of TNF-α. Given the increase in TNF-α seen in the olfactory epithelium of former COVID-19 patients recovering their sense of smell, vitamin C and E have the potential to support their recovery. In the cases where patients do not recover their sense of smell, supplementation of vitamin C and E can serve as prospective therapies that assist in their recovery.

Vitamin D

The general functions of vitamin D have been extensively studied; it is known to play an important role in maintaining calcium levels. Furthermore, it is linked to many inflammatory diseases. Vitamin D carries the unique ability to be produced by the skin through exposure to sunlight [28]; however, it is often taken up through limited dietary sources and supplements [29]. The active form of vitamin D is known to have immunomodulatory functions that help treat and prevent infectious diseases [30]. This is achieved through various immune cells, including macrophages, dendritic cells, and activated T cells that express the intracellular vitamin D receptor. Vitamin D reduces T helper type 1 (Th1) immune responses. Th1 cells produce proinflammatory cytokines, tumour necrosis factor-β, and IFN- γ. In a study conducted by Grant, et al. [31], a key observation was the decrease in the production of proinflammatory Th1 cytokines, such as TNF-α, and IFN- γ. Likewise, a study conducted by Jeffery et al. [32] noted inhibition of T cell inflammatory cytokine production, specifically, a decrease in the cells producing IFN- γ. A report by Kruse and Cambron [33] presented two cases of an increased ability to smell after intervention through vitamin D supplements.

Multiple studies have reported vitamin D as a crucial regulator in reducing the production of inflammatory cytokines; TNF-α being one. The decrease in production of these proinflammatory enzymes can potentially aid in the recovery of smell for post-COVID-19 infected individuals. Thus, a potential therapy for the recovery of olfaction can be developed by the supplementation of vitamin D through diet.

Omega-3 Polyunsaturated Fatty Acids

Omega-3 fatty acids are a class of polyunsaturated fatty acids (PUFAs) which are named after a carbon-carbon double bond that is located at the third carbon from the methyl end. Along with their involvement in crucial cellular functions and numerous physical health benefits, omega-3 fatty acids such as alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) also have anti-inflammatory properties [34]. These fatty acids can decrease inflammation through various mechanisms [35]. One being, DHA and EPA construct various anti-inflammatory lipid mediators such as resolvins and protectins [35]. Kang and Weylandt [36] suggest that these mediators greatly decrease the activity of the NF-κB transcription factor which is responsible for the induction of pro-inflammatory cytokines such as TNF-α [36]. This results in the decrease of TNF-α, aiding in the reduction in inflammation [36].

Therefore, the anti-inflammatory nature of omega-3 fatty acids provides them the potential to become a dietary intervention for the recovery of anosmia and olfaction dysfunction for individuals post-COVID-19.

CONCLUSION

The loss and dysfunction of olfaction due to SARS-CoV-2 has been reported to recover within weeks [5]. However, many studies have identified long-term complications of olfaction [4,6]. Clinical studies have observed elevated levels of pro-inflammatory TNF-α in the olfactory epithelium of COVID-19 positive individuals [9]. The direct inflammation of olfactory epithelium can affect an individual's ability to smell [9]. Given the ineffectiveness of corticoid treatments in recovering [12], this review focused on dietary supplements with anti-inflammatory properties to attenuate the loss of smell. Vitamin C, vitamin E, vitamin D, and omega-3 fatty acids have been reported to target TNF-α activity. The supplementation of these nutrients has led to a decrease in TNF-α levels in numerous studies. Future clinical studies should focus on the effectiveness of these dietary supplements in recovering olfaction post-COVID-19. Precisely, further studies should evaluate the effect of dietary supplements and foods containing vitamin C, vitamin D, vitamin E, and omega-3 fatty acids in mitigating the production of TNF-α to reduce inflammation within olfactory epithelium. Dietary supplements that are successful in reducing inflammation in the olfactory epithelium and in returning the sense of smell can then be used as the foundation to develop a dietary treatment to help individuals recover olfaction.

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COMPETING INTERESTS

The authors declare no competing interests with this case.

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