Pak. J. Chest Med. 2021;27(04)

Review Article

journal homepage: https:/www.pjcm.net/

Pakistan Journal of Chest Medicine

Official journal of Pakistan Chest Society

The Physiologic and biochemical Effects of Vitamin C in Patients with Chronic Obstructive Pulmonary Disease: A Systematic Review

Asma Inam[1]✉, Nazish Sadiq[2], Summyah Niazi[3], Rakhshanda Naheed[4], Amber Asfandyar[1], Fouzia Qadir[5]

[1]Department of Physiology, Khyber Medical College, Peshawar - Pakistan [2]Department of Biochemistry, Rehman College of Dentistry, Peshawar - Pakistan [3]Department of Physiology, Quetta institute of Medical Sciences, Quetta - Pakistan [4]Department of Physiology, Loralai Medical College, Loralai - Pakistan [5]Department of Biochemistry, North West School of Medicine, Peshawar - Pakistan

Corresponding Author:
Asma Inam
Department of Physiology,
Khyber Medical College,
Peshawar - Pakistan
Email: asmainam9900@gmail.com

Article History:

Received:	Jun 09, 2021
Revised:	Sep 21, 2021
Accepted:	Nov 12, 2021
Available Online:	Dec 02, 2021

Author Contributions:
AI conceived idea, NS SN drafted the study, RN AA collected data, FQ AI did critical reviewed manuscript. All approved final version to be published.

Declaration of conflicting interests:
All authors declare that they have no conflict of interest.

How to cite this article:
Inam A, Sadiq N, Niazi S, Naheed R, Asfandyar A, Qadir F. The Physiologic and biochemical Effects of Vitamin C in Patients with Chronic Obstructive Pulmonary Disease: A Systematic Review. Pak J Chest Med. 2021;27(04):364-372.

A B S T R A C T

Background: The versatile functions of antioxidants in a variety of health conditions have garnered a lot of interest lately. Popular for its antioxidant properties, vitamin C has been utilized to treat people suffering from chronic obstructive pulmonary disease (COPD). The purpose of this systematic review is to show how vitamin C supplements benefit COPD patients.

Objective: To look into how vitamin C might help with chronic obstructive pulmonary disease (COPD).

Methodology: We conducted a systematic review and meta-analysis to evaluate the effect of vitamin C on chronic obstructive pulmonary disease (COPD) by analyzing randomized controlled trials (RCTs) from Cochrane Library, Embase, PubMed, Scopus, and Web of Science up to August 1, 2020. Studies included were English-language RCTs involving adult COPD patients who received vitamin C supplementation versus placebo, reporting on serum antioxidants, nutrition, and lung function. Exclusion criteria encompassed studies with comorbidities, non-human experiments, reviews, case reports, and articles with insufficient data.

Results: A literature search identified 1268 studies, with 189 duplicates. Studies varied in vitamin C dosage and duration, and most assessed lung function (FEV1% or FEV1/FVC) and serum antioxidant levels. Subgroup analysis showed significant improvement in FEV1% with (≥400 mg/day of vitamin C) (SMD: 1.10, P = 0.03), but no significant change with <400 mg/day. Sensitivity analysis revealed that one study (Long et al.) had a substantial impact on results. “Serum vitamin C levels were higher in the vitamin C group (SMD: 0.64, P = 0.03), while vitamin E levels showed no significant difference (SMD: 0.84, P = 0.08). Serum GSH was significantly higher with vitamin C (SMD: 2.46, P = 0.0007), with significant variation among studies. SOD levels showed no difference (SMD: 0.43, P = 0.72), and vitamin C had no significant effect on BMI or FFMI.

Conclusion: The present study suggest that vitamin C supplements have important clinical implications for COPD patients. Reduced oxidative lung damage means increased lung function and elevated serum antioxidant levels. In the meantime, we discovered that vitamin C administration might raise the serum level of antioxidants in COPD patients, but not their nutritional status.

Keywords: COPD; Vitamin C; RCTs; Review

Copyright:© 2021 by author(s) and PJCM 2021. This is an open access article distributed under the terms of the Creative Commons Attribution License, (http://creativecommons.org/licenses/by-nc-nd/4.0/) which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited

Introduction

Currently, the third most common cause of death globally is chronic obstructive pulmonary disease, or COPD.1 Because of the growing social and financial costs involved, comprehensive control is a key objective for public health.[1-3] Prolonged breathing problems and airflow restriction are characteristics of COPD. These signs and symptoms are caused by airway and/or aberrations of the alveoli, which are typically brought on by smoking fumes or prolonged exposure to dangerous particulates. The disruption of the oxidant/antioxidant equilibrium is known as oxidative stress, and it has been proposed that oxidative stress is a key factor in the pathophysiology of' COPD.[4-6] As the primary line of defence toward oxidants, antioxidants shield the lungs from the acute effects of reactive oxygen species and/or other oxidants.[7] The top three most often prescribed medications to treat flare-ups of COPD are short-acting 'bronchodilators, systemic corticosteroids, and antibiotics. However, there is no proof that these drugs prevent oxidative stress. In the meantime, because of their bodies' steroid resistance, the majority of COPD patients react badly to cortices.[8]

Vitamins that are high in vitamin C are popular because of its potent antioxidants.[9]It performs its antioxidant role by maintaining the matching decreased state of both long-lived oxidants, like semiquinone radicals, and transient oxidants, including O_2 and nitric oxide.[7,10,11] Assessing the clinical treatment impact of vitamin C administration in individuals with COPD' is our goal.

According to Kanani et al.'s study, adult lung function and vitamin C intake are positively correlated'.[12–14] Liu et al. (2013) found a negative link between the antioxidation level of vitamin C and SOD in blood and vitamin C supplements, however Gouzi et al.'s study showed a positive correlation between the two parameters.[15] Furthermore, despite the fact that many research investigations have demonstrated the link between COPD and malnutrition[16,17], there has been no discernible shift in body mass index (BMI) or fat-free mass index (FFMI) following 'vitamin C' treatment.

A critical aspect of COPD is oxidative stress, which involves exposure to oxidative compounds' like peroxide ions, OH radicals, and hydrogen peroxide, combined with a deficiency in antioxidants. Chronic illnesses like COPD are associated with these shortages in antioxidants. Patients with COPD experience worsening conditions due to oxidative stress, which damages endothelial alveoli and inactivates anti-proteases. Factors like smoking and air pollution further aggravate oxidative stress, contributing to the progression of COPD. Thus, managing oxidative stress through antioxidant supplementation could potentially aid in controlling COPD.

Objective

To look into how vitamin C might help with chronic obstructive pulmonary disease (COPD).

Mathodology

We searched the Web of Science, Cochrane Library, Embase, PubMed and Scopus for randomized controlled trials (RCTs) that looked into the effect of vitamin C on chronic obstructive pulmonary disease (COPD). The search was restricted to research written in 'English only, with no other constraints, and it encompassed all records up to August 1, 2020. The records were screened and managed using Endnote X9 software.

Relevant studies were evaluated for inclusion by two researchers and any differences were discussed and settled with an additional researcher. 18–20 The following were the requirements for inclusion:

(1) COPD-diagnosed patients who were 18 years of age or older were included in the eligible studies;

(2) vitamin C supplementation was contrasted with a placebo in the research; and

(3) randomized controlled trials (RCTs) that reported data on serum antioxidants, nutrition, and lung function were included in the studies. Based on each qualifying study, the two researchers separately gathered the following data: investigation time span, demographics of participants, methodology, country of origin, vitamin C consumption, and first author.

Results

A literature search using the specified approach turned up 1268 studies, 189 of which were duplicates. 24 publications were selected for full-text review out of 1055 papers that were excluded after title and abstract reviews. In the end, eleven articles met the criteria for this investigation.[6,13–15,22–27] Each investigation included a sufficient random sequence generation procedure and was RCT. Seven research[6,13,14,22,24,26] explained how hiding allocations was done. In total, 247 individuals who got vitamin C therapy and 238 individuals who got placebos were incorporated in the current meta-analysis, for a total of 485 participants. Men patient reports have been included in four investigations,[13,14,23,26] and a further four research [6,15,22,24]and the 'male-female ratio'. However, both investigations [25, 27] did not disclose the patients' sex. Participants received daily 'vitamin C supplements of less than 400 mg/day' in two studies[6,15] but patients in the other trials received vitamin C supplements of 400 mg/day or more.[13,14,22,27] The function of the lungs was the main outcome in seven studies.[6,13,14,22,24–26] Serum antioxidation levels were reported in eight research[6,13–15,22–24,27] whereas 'three studies reported nutritional status[15,23,27] as

Table 1. Features Of Involved Investigations

Researches	Research design	Region	Categories	Participant number	Treatment	Initial Results	Secondary Results	Time span of monitoring
Wu et al. (2006)	RCT	China, Taiwan	Vitamin C	8	Vitamin C 250 mg/d	ab	ef	12 weeks
			Placebo	9	Placebo			
Ansari and colleagues (2010)	RCT, Single blind	Pakistan	Vitamin C	23	Vitamin C 1000 mg/d	ab	NA	36 weeks (9 months)
			Placebo	22	Salbutamol 100 µg and beclomethasone 50 µg			
Liu and colleagues (2010)	RCT, Double blind	China, Taiwan	Vitamin C	11	Vitamin C 500 mg/d + Vitamin E 400 IU/d	ab	efh	13 weeks
			Placebo	8	Vitamin E 400 IU/d			
Kanani and colleagues (2012)	RCT	India	Vitamin C	17	Vitamin C 500 mg/d + Vitamin E 200 mg/d	ab	g	12 weeks (3 months)
			Placebo	15	Vitamin E 200 mg/d			
Long and colleagues (2013)	RCT	China	Vitamin C	24	Conventional therapy + exercise + Vitamin C 400-800 mg/d + VE 8-10 IU/d	a	ef	NA
			Placebo	19	Conventional therapy + exercise			

Zou and colleagues. (2015)	RCT	China	Vitamin C	57	Vitamin C 300-600 mg/d	ab	NA	24 weeks (6 months)
			Placebo	58	Nothing			
Pirabbasi and colleagues (2016)	RCT, Single blind	Malaysia	Vitamin C	12	Vitamin C 500 mg/d	NA	cfefg	24 weeks (6 months)
			Placebo	17	NA			
Chen and colleagues (2016)	RCT	China	Vitamin C	25	Conventional therapy + Vitamin C 500 mg/d	a	gh	20 days
			Placebo	25	Conventional therapy			
Jia and colleagues (2017)	RCT	China	Vitamin C	25	Vitamin C 1500 mg/d	NA	cdefg	24 weeks (6 months)
			Placebo	25	Blank control group			
Gouzi and colleagues (2019)	RCT, Double blind	France	Vitamin C	32	Vitamin C 180 mg/d	NA	cdefh	28 days
			Placebo	25	Placebo			

secondary outcomes'. Table 1 displays the details of the reported randomized controlled trials.

With the exception of the Zou et al. study[25] there was little chance of 'bias in allocation concealment' in the other investigations. In terms of inadequate outcome data and potential bias, the risk of bias was minimal for all included RCTs (100%) in the analysis. Regarding the results of selective reporting, there was a fifty percent chance of bias in five research[13,22–25], while the remaining studies had a minimal risk of bias.

One of the objectives of COPD evaluation is to figure out the degree of airway limitation.1. The diagnosis can only be made using spirometry. The existence of chronic airflow restriction can be diagnosed using FEV1%.1,6 The vitamin C supplements given to COPD patients had an impact on these two diagnostic criteria. All the ten research studies that met the eligibility criteria, [6,13-15, 22-27] reported lung function as a result using the FEV1/FVC.[6,13,14,22,24-26]

The findings of the sensitivity analysis demonstrated that the Long et al.[24] study had a substantial impact on the pooled results. The study's I2 decreased from 86% to 0% if it was removed from our evaluation. We were careful not to exclude this study from our evaluation. In contrast to the placebo therapies employed in the other research that were reviewed, the Long et al study found that respiratory rehabilitation exercises by itself would not significantly improve pulmonary function in COPD patients in practical practice.[15] Our conclusion was that the practice of breathing may not have been the primary cause of the

variability.

Five studies (n=233 patients) examined the FEV1/FVC ratio; the results showed significant variation among these investigations (I2=97%, P<0.00001), with (SMD:0.67, 95% CI: 0.27,1.07, P=0.002). 'Sensitivity analysis revealed that none of the individual studies had a statistically significant impact on the combined data's outcomes.

Various studies assessed different antioxidants. The levels of vitamin C and vitamin E in serum' were tested in six studies including 230 patients and four studies involving 184 patients. GSH levels were detected.[14,22,23,27]

In the lung, non-enzymatic antioxidants include GSH, C, and E. Three investigations including 137 patients assessed the lung's amount of SOD, an enzyme antioxidant.[13,15,22]

Six 'investigations examined the serum levels of vitamins C and E in 119 individuals with COPD who received vitamin C and 110 patients who received a placebo.[6,13,15,23,24,27]

'Serum vitamin C levels were greater in the vitamin C group than in the placebo group, according to the pooled data from the six trials (SMD:0.64, 95% CI: 0.03, 1.25, P=0.03). There was also a considerable amount of variation between the studies (I2=79%, P=0.0003).

The findings on serum vitamin E levels were analyzed using a random effect model, and the results showed that there was substantial variation among these research investigations I2=90%, P<0.00001), with the 'serum vitamin E level being higher in the (vitamin C supplementation group than in the placebo group (SMD:0.84, 95% CI: –0.09, 1.75, P=0.08). .

Serum GSH levels were assessed in four RCTs with 184 patients.[14,22,23,27] Serum GSH is an important non-enzymatic antioxidant in the lung. The vitamin C supplementation group had greater serum GSH levels than the placebo group (SMD: 2.46, 95% CI: 1.07, 3.88, P=0.0007), according to pooled data. There was also significant variation among the studies I2=96%, P<0.00002. Based on the length of treatment, subgroup analysis showed that vitamin C significantly increased GSH levels in each of the subgroups. Sensitivity analysis showed that the results were greatly impacted by the study of Kanani et al.[14] This study was unique in that it treated patients with both vitamin C and vitamin E, as opposed to earlier studies that solely employed vitamin C. Although vitamin E may help lower oxidative stress and airway inflammation, there is no proof that it has an effect on serum GSH levels. Kanani's work thus remained in its entirety.

Discussion

Each year, COPD claims the lives of about 3 million individuals worldwide, although little progress has been made in delaying the course of the illness or lowering mortality.[17] It has been proposed that oxidative stress, which is caused by an imbalance between antioxidants and oxidants, plays a major factor in the pathophysiology of COPD.[4–6] Overexposure to oxidants can cause oxidative tissue damage, inactivation of antiproteases, and upregulation of genes linked to inflammation, all of which can result in COPD.[29] It has been demonstrated that a number of variables, such as smoking and air pollution, might raise systemic oxidative stress in COPD patients.[30]

The onset of COPD is linked to an excess of oxidant exposure and/or a reduction in antioxidant levels. Smoking is a prime example. Many oxidants, including various free radicals, were discovered among the more than 4000 components of cigarette smoke that have been identified. These constituents may be the cause of the increased oxidative stress that smokers with COPD experience.[30, 31] Taking supplements of antioxidants may help with COPD symptoms.6 One popular antioxidant supplement is vitamin C. Research has demonstrated that administering vitamin C supplements to patients with COPD can reduce the harm caused by excessive oxidative stress.[9] These findings remained unchanged after sensitivity analyses that eliminated low-quality papers were performed. By means of the subgroup analysis, we discovered that, when taken in the appropriate dosage, vitamin C supplements beyond 400 mg/day considerably enhanced lung performance, whereas vitamin C supplements under 400 mg/day did not significantly affect lung function in any way.

The findings demonstrated that vitamin C supplementation significantly raised the serum level of GSH in every subgroup that was examined. There was no discernible variation observed between the subgroups for the elevation of GSH levels in serum. The body of research indicates that vitamin C supplementation helps treat COPD in a way that is clinically significant. Uncertainty surrounds the exact method by which vitamin C supplements enhance lung function[7–9] According to research by Liu et al., vitamin C supplements help COPD patients breathe easier and feel better. According to Wu et al., lung function and dietary antioxidant levels, such as vitamin C, were favourably connected, but whether this was was unclear whether it was also helpful in the treatment of COPD, which ran counter to the findings of multiple other investigations. The FEV1/FVC ratio in COPD patients was shown to be significantly reduced by salbutamol and beclomethasone treatments.[13,14,22,24,25] However, a small but not statistically significant decrease in the ratio of FEV1/FVC was noted when vit C therapy was added.[26]

The findings of our meta-analysis suggest that vitamin C supplements may help COPD patients' lung function which was in accordance with other investigations.[32-35] The rationale for this development could be numerous. However, its antioxidant capacity might be the most significant. With COPD, oxidative overloading is a common occurrence that is mostly brought on by

infection and hypoxia. It is essential to the remodeling and deterioration of lung tissue. As an antioxidant, vitamin C antioxidant, has been utilized extensively in a variety of illnesses that have pathophysiologic traits with conditions like ARDS, sepsis, etc.[36,37]

Vitamin C has been shown to be a highly efficient attenuator of oxidative stress, which may inhibit the lung structure remodeling.[38] For example, raised oxidative stress can result in dysregulated antiproteases in lung tissue, which is central to the pathophysiology of COPD-related emphysema.[39] Furthermore, it has been discovered that oxidative stress has a mechanistic role in pulmonary fibrosis. Research indicates that a disparity in reactive ROS/RNS, causes several pro-fibrotic molecules, such TGF-β, to be overexpressed.[40] Although there are a number of theories that could account for the beneficial effects of vitamin C on lung function, direct research examining these correlations is currently lacking. This is an issue that requires more discussion.

The levels of key plasma antioxidants Vitamin E, Vitamin C, and GSH are lower in smokers than in nonsmokers.[14,41] A class of metalloenzymes known as superoxide dismutases (SODs) is responsible for converting O2–to H2O2. Hydroxygenase and glutathione peroxidase convert H2O2 into oxygen and water.[28, 29, 42] An investigation by Peh et al. demonstrated that oxidative stress was elevated when the activities of these three important antioxidant enzymes were inhibited, which raised the risk of emphysema.[28] An antioxidant that is often employed is vitamin C. Apart from serving as vitamin C plays a crucial role in breaking down chains of antioxidants in the aqueous phase.[43] When there is an increase in the formation of free radicals in bodily fluids, electron spin resonance can quickly deplete vitamin C.[44] This is a process that vitamin C mediates in the antioxidation process. The DNA break was considerably reduced after vitamin C supplementation,[6] creating a favourable environment for the regeneration of GSH radicals.[45] Vitamin E's main role is to act as an antioxidant that breaks chains.[46] To raise the amount of non-oxidized vitamin E in the blood, vitamin C can help convert oxidized vitamin E into non-oxidized vitamin E.[47,48] Additionally, vitamin C and vitamin E showed complementary effects in terms of antioxidant activity.[28] Increasing serum vitamin E was shown to be preventive against COPD mortality by Hanson et al.[46,49]

Throughout COPD therapy, malnutrition is a concern that is frequently disregarded.[50] Weight loss and protein and calorie malnutrition affect 20–50% of COPD patients, which can worsen the disease, cause respiratory muscle dysfunction, increase disability, and ultimately increase the disease's mortality.[17,51] Mete et al. discovered that COPD patients with low body mass index and malnutrition had considerably worse lung function.50 Similarly, it was discovered that individuals with COPD who had low body mass indices as well as those who were malnourished or at risk of malnourishment had considerably smaller amounts of fat-free body mass.[50] Reduced FFMI may have detrimental physiologic effects on COPD patients.[52, 53] These suggested that FFM and total body mass are significant predictive variables for COPD.

An excess of free radicals can cause systemic inflammation, which can harm muscles and bones, impair breathing ability, and impair lung function.[54,55] Conversely, oxidative stress plays a significant role in the pathophysiology of COPD and ultimately leads to impaired respiratory function.[27] A sedentary lifestyle brought on by the restricted gas exchange will inevitably result in a low-antioxidant diet and a decrease in appetite and nutrient content. The resulting malnutritional status would worsen the patients' pre-existing malnourishment and heighten the severity of the disease. It would also accelerate the progression of the disease and raise oxidative stress in the patients.[54,56]

Numerous investigations demonstrated that oxidative stress was, in fact, a detrimental element contributing to the atrophy and malfunctioning of muscles in patients with COPD.[15,57] Antioxidants are essential for enhancing muscular atrophy and endurance in COPD patients.[59] Gouzi et al. pointing out that vitamin C was ineffective as a pulmonary rehabilitation supplement.[15] Low body mass index (BMI) and fat-free mass index (FFMI) characteristics were linked to a poor outcome in the COPD population, according to a Cochrane systematic review.[60] These outcomes are in line with our investigations, which suggest that vitamin C treatment may enhance the nutritional situation in COPD patients.

Conclusion

Finally, we discovered that vitamin C supplements have important clinical implications for COPD patients. Reduced oxidative lung damage means increased lung function and elevated serum antioxidant levels. In the meantime, we discovered that vitamin C administration might raise the serum level of antioxidants in COPD patients, but not their nutritional status. Large-scale, carefully planned prospective RCTs are required to corroborate these results further.

References

1. Prevention GSF. Global initiative for chronic obstructive lung disease; 2020. Available from URL: https://goldcopd.org/wp .
2. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the global burden of disease study 2010. Lancet. 2012;380(9859):2095–2128. DOI:10.1016/S0140 6736(12)61728-0.

3. Vos T, Flaxman AD, Naghavi M. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the global burden of disease study 2010. Lancet. 2012;380(9859):2163-96. DOI:10.1016/S0140 6736 (12)61729-2.
4. MacNee W. Pulmonary and systemic oxidant/ antioxidant imbalance in chronic obstructive pulmonary disease. Proc Am Thorac Soc. 2005;2 (1):50–60. DOI:10.1513/pats. 200411-056SF.
5. Morrison D, Rahman I, Lannan S, MacNee W. Epithelial permeability, inflammation, and oxidant stress in the air spaces of smokers. Am J Respir Crit Care Med. 1999;159(2):473–479. DOI:10.1164/ ajrccm.159.2.9804080.
6. Wu TC, Huang YC, Hsu SY, Wang YC, Yen SL. Vitamin E and vitamin C supplementation in patients with chronic obstructive pulmonary disease. Int J Vitam Nutr Res. 2007;77(4):272–79. DOI:10.1024/0300-9831.77.4.272.
7. Rahman I, Biswas SK, Kode A. Oxidant and antioxidant balance in the airways and airway diseases. Eur J Pharmacol. 2006;533(1–3):222–39. DOI:10.1016/j.ejphar. 2005.12.087.
8. Barnes PJ, Ito K, Adcock IM. Corticosteroid resistance in chronic obstructive pulmonary disease: inactivation of histone deacetylase. Lancet. 2004; 363(9410):731-3. DOI:10.1016/S0140-6736(04) 15650-X.
9. Romieu I, Trenga C. Diet and obstructive lung diseases. Epidemiol Rev. 2001;23(2):268-87. DOI:10.1093/oxfordjournals.epirev.a000806.
10. Church DF, Pryor WA. Free-radical chemistry of cigarette smoke and its toxicological implications. Environ Health Perspect. 1985;64:111-26. DOI:10. 1289/ehp.8564111
11. Nakayama T, Church DF, Pryor WA. Quantitative analysis of the hydrogen peroxide formed in aqueous cigarette tar extracts. Free Radic Biol Med. 1989;7 (1):9–15. DOI:10.1016/0891-5849(89)90094-4.
12. Shaheen SO, Jameson KA, Syddall HE. The relationship of dietary patterns with adult lung function and COPD. Eur Respir J. 2010;36 (2):277-84. DOI:10.1183/09031936.00114709.
13. Liu LC, Huang CY, Huang JJ, Lee HC, Huang SY. The effect of vitamin C & E supplement on the antioxidative status in patients with chronic obstructive pulmonary disease: a double-blind placebo-control pilot study. Nutr Sci J. 2010;35(2):65-76.
14. Kanani NJ, Patel SA, Hotchandani SC, Bhatt JD. A study of efficacy of antioxidant therapy in the management of chronic obstructive pulmonary disease. Res J Pharm Biol Chem Sci. 2012;3(4):1071-8.
15. Gouzi F, Maury J, Héraud N. Additional effects of nutritional antioxidant supplementation on peripheral muscle during pulmonary rehabilitation in COPD patients: a randomized controlled trial. Oxid Med Cell Longev. 2019:5496346. DOI:10.1155/2019/ 5496346.
16. McNicholas WT. COPD-OSA overlap syndrome: evolving evidence regarding epidemiology, clinical consequences, and management. Chest. 2017;152 (6):1318–1326. DOI:10.1016/j.chest. 2017.04.160.
17. Rabe KF, Watz H. Chronic obstructive pulmonary disease. Lancet. 2017;389(10082):1931-40. DOI:10.1016/S0140-6736(17)31222-9.
18. Fu Y, Zha S, Lü N, et al. Carrier frequencies of hearing loss variants in newborns of China: a meta-analysis. J Evid Based Med. 2019;12(1):40–50. DOI:10.1111/ jebm.12305.
19. Long Y, Hu T, Liu L. Effectiveness of N95 respirators versus surgical masks against influenza: a systematic review and meta-analysis. J Evid Based Med. 2020;13(2):93–101. DOI:10.1111/jebm.12381.
20. Pan B, Ge L, Xun YQ. Exercise training modalities in patients with type 2 diabetes mellitus: a systematic review and network meta-analysis. Int J Behav Nutr Phys Act. 2018;15(1):72. DOI:10.1186/s12966-018-0703-3.
21. Higgins JPT, Green S Cochrane handbook for systematic reviews of interventions version 5.0.1; 2008.
22. Chen M, Zhixian J, Hong B, Junyi D. Research of vitamin C in the treatment of patients with AECOPD. J Clin Pulm Med. 2016;2016(3):456-9.
23. Jia T, Jian H. Effect of antioxidants supplementation on nutritional and antioxidant status of chronic obstructive pulmonary disease patients. J Clin Pulm Med. 2017;22(11):2009-13.
24. Long Z. Chronic obstructive pulmonary disease patients breathing muscle recovery and vitamin D, E relationship. Natl Med Front China. 2013;20; (21):25-6.
25. Zou Y, Fengping L. Influence of antioxidant vitamins combined with moderate protein diet on lung function and quality of life of COPD patients in stable phase. Chin Nurs Res. 2015;29(10B):1.
26. Ansari MA, Ansari S, Memon Z. Does antioxidant ascorbic acid supplementation delay lung function deterioration in stable patients with chronic obstructive? Pulmonary disease. Rawal Med J. 2010;35 (2):133-6.
27. Pirabbasi E, Shahar S, Manaf ZA, Rajab NF, Manap RA. Efficacy of ascorbic acid (vitamin C) and/N-

Acetylcysteine (NAC) supplementation on nutritional and antioxidant status of male Chronic Obstructive Pulmonary Disease (COPD) Patients. J Nutr Sci Vitaminol. 2016;62(1):54-61. DOI:10.3177/jnsv.62.54

28. Peh HY, Tan WSD, Chan TK, Pow CW, Foster PS, Wong WSF. Vitamin E isoform γ-tocotrienol protects against emphysema in cigarette smoke- induced COPD. Free Radic Biol Med. 2017;110:332-4. DOI:10.1016/j.freeradbiomed. 2017.06.023
29. Drost EM, Skwarski KM, Sauleda J, et al. Oxidative stress and airway inflammation in severe exacerbations of COPD. Thorax. 2005;60 (4):293–300. DOI:10.1136/thx.2004.027946.
30. Saad A, Mostafa A, Ibrahim K. Role of natural juice in improving the ventilatory functions of smokers with chronic obstructive pulmonary disease. J Nutr Environ Med. 2007;16(1):16-25. DOI:10.1080/13590840701211219.
31. Marangon K, Herbeth B, Lecomte E, et al. Diet, antioxidant status, and smoking habits in French men. Am J Clin Nutr. 1998;67(2):231–239. DOI:10.1093/ajcn/67.2.231.
32. Schwartz J, Weiss ST. Relationship between dietary vitamin C intake and pulmonary function in the first National Health and Nutrition Examination Survey (NHANES I). Am J Clin Nutr. 1994;59(1):110-4. DOI:10.1093/ajcn/59.1.110
33. Britton JR, Pavord ID, Richards KA. Dietary antioxidant vitamin intake and lung function in the general population. Am J Respir Crit Care Med. 1995;151(5):1383-7. DOI:10.1164/ajrccm.151.5.7735589.
34. Hu G, Zhang X, Chen J, Peto R, Campbell TC, Cassano PA. Dietary vitamin C intake and lung function in rural China. Am J Epidemiol. 1998; 148(6):594-9. DOI:10.1093/oxfordjournals.aje.a009685.
35. Chen R, Tunstall-Pedoe H, Bolton-Smith C, Hannah MK, Morrison C. Association of dietary antioxidants and waist circumference with pulmonary function and airway obstruction. Am J Epidemiol. 2001;153 (2):157-63. DOI:10.1093/aje/153.2.157.
36. Carr AC, Shaw GM, Fowler AA, Natarajan R. Ascorbate dependent vasopressor synthesis: a rationale for Vitamin C administration in severe sepsis and septic shock? Critic Care. 2015;19: 1-8. DOI: 10.1186/s13054-015-1131-2.
37. Boretti A, Banik BK. Intravenous vitamin C for reduction of cytokines storm in acute respiratory distress syndrome. PharmaNutrition. 2020;12: 100190. DOI:10.1016/j.phanu. 2020.100190.
38. Boritti A, Banik BK. Intravenous vitamin C for reduction of cytokines storm in acute respiratory distress Syndrome. Pharam Nut. 2020;12:100190.
39. Mizumura K, Maruoka S, Shimizu T, Gon Y. Autophagy, selective autophagy, and necroptosis in COPD. Int J Chron Obstruct Pulmon Dis. 2018;13: 3165-72. DOI:10.2147/COPD.S175830.
40. Fois AG, Paliogiannis P, Sotgia S, Mangoni AA, Zinellu E, Pirina P, et al. Evaluation of oxidative stress biomarkers in idiopathic pulmonary fibrosis and and therapeutic applications: a systematic review. Respir Res. 2018;19:1-3.
41. Caliko lu M, Unlü A, Tamer L, Ercan B, Bu dayci R, Atik U. The levels of serum vitamin C, malonyldialdehyde and erythrocyte reduced glutathione in chronic obstructive pulmonary disease and in healthy smokers. Clin Chem Lab Med. 2002;40 (10):1028-31. DOI:10.1515/ CCLM.2002.179.
42. Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med. 2004;350(10):1005-12. DOI:10.1056/NEJMoa021322.
43. Jialal I, Vega GL, Grundy SM. Physiologic levels of ascorbate inhibit the oxidative modification of low density lipoprotein. Atherosclerosis. 1990;82(3): 185-91. DOI:10.1016/0021-9150(90)90039-L.
44. Pietri S, Séguin JR, D'Arbigny PD, Culcasi M. Ascorbyl free radical: a noninvasive marker of oxidative stress in human open-heart surgery. Free Radic Biol Med. 1994;16(4):523-8. DOI:10.1016/0891-5849(94)90131-7.
45. De Flora S, Bennicelli C, Camoirano A, et al. In vivo effects of N-acetylcysteine on glutathione metabolism and on the biotransformation of carcinogenic and/or mutagenic compounds. Carcinogenesis. 1985;6(12):1735-45. DOI:10.1093/carcin/6.12.1735.
46. Hanson C, Lyden E, Furtado J. Serum tocopherol levels and vitamin E intake are associated with lung function in the normative aging study. Clin Nutr. 2016;35(1):169-74. DOI:10.1016/j.clnu.2015.01.020.
47. Ives SJ, Harris RA, Witman MA, et al. Vascular dysfunction and chronic obstructive pulmonary disease: the role of redox balance. Hypertension. 2014;63(3):459-67. DOI:10.1161/HYPERTENSIONAHA.113.02255.
48. Rossman MJ, Groot HJ, Reese V, Zhao J, Amann M, Richardson RS. Oxidative stress and COPD: the effect of oral antioxidants on skeletal muscle fatigue. Med Sci Sports Exerc. 2013;45(7):1235-43. DOI:10.1249/MSS.0b013e3182846d7e.

49. Walda IC, Tabak C, Smit HA, et al. Diet and 20-year chronic obstructive pulmonary disease mortality in middle-aged men from three European countries. Eur J Clin Nutr. 2002;56(7):638-43. DOI:10.1038/sj.ejcn.1601370.
50. Mete B, Pehlivan E, Gülba G, Günen H. Prevalence of malnutrition in COPD and its relationship with the parameters related to disease severity. Int J Chron Obstruct Pulmon Dis. 2018;13:3307–3312. doi:10.2147/COPD.S179609
51. Hillas G, Perlikos F, Tsiligianni I, Tzanakis N. Managing comorbidities in COPD. Int J Chron Obstruct Pulmon Dis. 2015;10:95-109. DOI:10.2147/COPD.S54473.
52. Heitmann BL, Erikson H, Ellsinger BM, Mikkelsen KL, Larsson B. Mortality associated with body fat, fat-free mass and body mass index among 60-year-old Swedish men-a 22-year follow-up. The study of men born in 1913. Int J Obes Relat Metab Disord. 2000;24(1):33-7. DOI:10.1038/sj.ijo.0801082.
53. Bigaard J, Frederiksen K, Tjønneland A. Body fat and fat-free mass and all-cause mortality. Obes Res. 2004;12(7):1042-9. DOI:10.1038/oby.2004.131.
54. Agustí AG, Noguera A, Sauleda J, Sala E, Pons J, Busquets X. Systematic effects of chronic obstructive pulmonary disease. Eur Respir J. 2003;21(2):347-60. DOI:10.1183/09031936.03.00405703.
55. Agustí AG, Sauleda J, Miralles C. Skeletal muscle apoptosis and weight loss in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2002;166(4):485-9. DOI:10.1164/rccm.2108013.
56. Agusti AG. COPD, a multicomponent disease: implications for management. Respir Med. 2005;99(6):670-82. DOI:10.1016/j.rmed.2004.11.006.
57. Maltais F, Decramer M, Casaburi R, et al. An official American Thoracic Society/European Respiratory Society statement: update on limb muscle dysfunction in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2014;189(9):e15–62. DOI:10.1164/rccm.201402-0373ST.
58. Koechlin C, Couillard A, Simar D, et al. Does oxidative stress alter quadriceps endurance in chronic obstructive pulmonary disease? Am J Respir Crit Care Med. 2004;169(9):1022-7. DOI:10.1164/rccm.200310-1465OC.
59. Pomiès P, Blaquière M, Maury J, Mercier J, Gouzi F, Hayot M. Involvement of the FoxO1/MuRF1/Atrogin-1 signaling pathway in the oxidative stress-induced atrophy of cultured chronic obstructive pulmonary disease myotubes. PLoS One. 2016;11(8):e0160092. DOI:10.1371/journal.pone.0160092.
60. Ferreira IM, Brooks D, White J, Goldstein R. Nutritional supplementation for stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2012;12:Cd000998. DOI:10.1002/14651858.CD000998.pub3.