Medical Science

pISSN 2321–7359; eISSN 2321–7367

Role of zinc, selenium, vitamin D and vitamin C in boosting respiratory system: A meta-analysis approach

Nazfar Nazari[1], Firoozeh Niazvand[2]✉, Narges Chamkouri[3], Neda Amoori[4], Mohsen Shafiee Asl[5]

To Cite:
Nazari N, Niazvand F, Chamkouri N, Amoori N, Asl MS. Role of zinc, selenium, vitamin D and vitamin C in boosting respiratory system: A meta-analysis approach. Medical Science, 2022, 26, ms77e1837.
doi: https://doi.org/10.54905/disssi/v26i121/ms77e1837

Author Affiliation:
[1]Student Research Committee, Abadan University of Medical Sciences, Abadan, Iran
[2]Assistant Professor, Department of Anatomical Sciences, Abadan University of Medical Sciences, Abadan, Iran
[3]Assistant Professor, Department of Biochemistry, Abadan University of Medical Sciences, Abadan, Iran
[4]Abadan University of Medical Sciences, Abadan, Iran
[5]Instructor of Geriatric Nursing, School of Nursing Abadan University of Medical Science, Iran

✉**Corresponding author**
Assistant Professor, Department of Anatomical Sciences, Abadan University of Medical Sciences,
Abadan, Iran
Email: niazvandf@gmail.com

Peer-Review History
Received: 16 November 2021
Reviewed & Revised: 17/November/2021 to 06/February/2022
Accepted: 07 February 2022
Published: 24 February 2022

Peer-review Method
External peer-review was done through double-blind method.

URL: https://www.discoveryjournals.org/medicalscience

DISCOVERY
SCIENTIFIC SOCIETY

ABSTRACT

Introduction: Respiratory tract infections consist of many diseases such as colds, pharyngitis, tonsillitis, influenza and respiratory diseases. Therefore, this meta-analysis study was performed to assay the effect of zinc, selenium, vitamin D, vitamin C on respiratory tract infections. *Methods:* In this systematic review of data on the effects of zinc, selenium, vitamin D and vitamin C on respiratory tract infections in the last 20 years in the world (2001-2020) with a review of 30 studies (5351 cases) including English and Persian articles, Reputable domestic and foreign sites were performed. Data were analyzed using meta-analysis. *Finding:* The odds ratio of respiratory tract infections in vitamin D users was estimated to be 0.797 (confidence interval 95%, 0.808-0.786). The Rate of odds of respiratory infections in consumers of vitamin C, 0.0496 (confidence interval 95%, 0.55-1.441) was estimated. The odds ratio of respiratory infections in zinc users was estimated to be 0.437 (confidence interval 95, 0.51-0.366). The odds ratio of respiratory tract infections in selenium users was estimated to be 0.624 (confidence interval 95, 0.696, 0.545). *Results:* Respiratory infections are seen in consumers of vitamin D, vitamin C, zinc, selenium. Proper use of vitamin D, vitamin C, zinc, and selenium is essential in addition to monitoring the epidemiology of regional respiratory infections.

Keywords: Vitamin D, vitamin C, zinc, selenium, respiratory infections

1. INTRODUCTION

Respiratory tract infections are such as colds, pharyngitis, tonsillitis, influenza and respiratory diseases (Banerjee et al., 2019; Farnoosh et al., 2020). Excessive respiratory tract infections are divided into two categories: 1- Lower respiratory tract infections (such as pneumonia, etc.), 2- Upper respiratory tract infections (such as colds, etc.), (Banerjee et al., 2019). Frequent and long-term infections in the lungs and chest cause prolonged inflammation. On the other hand, lung tissue is always Contains high amounts of oxygen, which, following any inflammation, is a type of oxygen molecule that is part of the species. This type of oxygen produced leads to an imbalance in many processes related to the function of alveolar epithelial cells and causes damage and injury to lung tissue. On the other hand, they can damage body tissues (oxidative damage). In this case, the body uses a variety of antioxidants and vitamins to protect itself against these damages. Vitamins and minerals have different and important functions in the body and reducing their level in the body affects the function of different parts of the body and can cause or aggravate some diseases. Vitamins are organic compounds that are essential for food metabolism, vital functions and growth. The presence of micronutrients, antioxidants, vitamins and maintaining their balance in the body is the main factor in maintaining the health of the immune system (Farnoosh et al., 2020; Cohen & Normile, 2020; Abduljawad, 2021). Various studies have shown that deficiency of some of these micronutrients reduces the function of the immune system and thus increases the incidence or exacerbation of infections. In general, it seems that the use of antioxidant compounds such as vitamin supplements and micronutrients along with the usual medications used by patients can reduce oxidative stress, which in turn will inhibit the spread of disease and reduce lung damage (Alimohamadi & Sepandi, 2020; Zhang et al., 2020).

Zinc is found in sources such as beef, almonds, legumes and eggs. Considering the positive effects of supplementation with vitamins D, C and selenium and zinc antioxidants in relieving and improving the symptoms of inflammation and infection of the respiratory tract and the mechanisms involved in inflammatory diseases in different ways, we decided to in this review, we evaluated the effect of zinc, selenium, vitamin C and vitamin D on strengthening the respiratory system.

2. MATERIALS AND METHODS

Search Strategy

Searching this meta-analysis study took place since January 2000 until December 2021. All the studies studied in this study were searched in Scopus, Science direct, Pubmed, Google scholar databases. Keywords in this study including zinc, selenium, vitamin D and vitamin C, respiratory infections in the United States, the United Kingdom, Canada, Sweden, Australia, Japan, the Netherlands, Finland, New Zealand, Bangladesh and Colombia. In this study, two researchers conducted a search strategy separately.

Selection of Studies

The articles studied in this study include the main published articles. 2- In order to prevent any bias, articles outside the scope as well as articles with duplicate results were excluded from this study. 3- In this study, in order to find the effect of zinc, selenium, vitamin D and vitamin C on respiratory system infections from cohort studies (prospective and retrospective), case-control and cross-sectional studies have been performed.

Quality Assessment

The STROBE checklist has been used to evaluate quality. This checklist consists of 22 sections that cover various aspects of methodology including study objectives, determining the appropriate sample size, type of study, sampling method, research community, data collection method, definition of variables and how to examine samples, data collection tools Covers statistical tests, study objectives, presenting findings appropriately and presenting results based on objectives. The minimum and maximum achievable scores are 0 and 44. According to the findings of quality evaluation, the researchers were classified in to three types: low quality (score less than 5.15), medium quality (score 29, 5-15, 5) and high quality (score 30-44). Studies with a quality rating score of less than 15, 5 were excluded from the meta-analysis.

Inclusion Criteria

All cross-sectional articles that reported the prevalence were included in this study, which included the incidence of respiratory tract infections with other infections among patients who received the required minimum score.

Exclusion criteria

Exclusion criteria in this study include: 1- Studies that have been case reports or series cases. 2. Studies that did not report a specific number of samples. 3. Studies that did not report co-occurrence of other infections with respiratory tract infections. 4 - Studies that were presented in the congresses and did not have a complete article. 5 - Studies that did not consider sufficient scores.

Data Extraction

In this meta-analysis study, authors' names, year of publication, place of study, country, number of samples, and sampling method were extracted and entered into Excel.

Statistical analysis

Odds ratio (OR) was used to measure the effect of exposure on the study outcome. All results were estimated and reported at 95% confidence level. Chi-square test at 10% confidence level (P less than 10%) was used for measurement the data heterogeneity in terms of quality. Statistical test I was also used to quantify the heterogeneity among the results (Field et al., 2002). If it is more than 50, it is a reflection of severe heterogeneity. Tau-squared statistical method was used for approximation of the variances of the studies. To analyze and integrate the results, statistical models of fixed effect or Mantel haenszel and Random effect (REM or Dersimonian-laird) were used. REM was calculated to investigate the heterogeneity among the studies. Comparison of extracted indices was used in the studies and the results were analyzed using Stata software.

3. RESULT

According to the results of Table 1-2, along of the heterogeneity of the studies and the significance of the heterogeneity index, the haphazard effects model was used in the meta-analysis. The heterogeneity of the stochastic effects model in this study was 98.86% (P <0.05). Therefore, the odds ratio of respiratory tract infections in vitamin D users between 2020-2000 was estimated to be 0.797 (95% confidence interval, 0.786_ 0.808) (Figures 1 and 2).

Table 1 Specifications of articles on the effect of vitamin D on respiratory infections

Row	Author	Country	Year of publication	Type of study	Number of samples	Age	Sex	OR
1	Aloia (2007)	America	2007	Case_Control	322	All age	M&F	0.31
2	Li-Ng (2009)	America	2009	Case_Control	162	All age	M&F	0.89
3	Laaksi (2010)	Finland	2010	RCT	164	18-28	M&F	0.76
4	Murdoch (2012)	New zealand	2012	Case_Control	322	All age	M&F	0.99
5	De Gruijl (2012)	Netherland	2012	RCT	105	18-30	M&F	0.86
6	Rees (2013)	England	2013	RCT	2259	45-75	M&F	0.93
7	Tran (2014)	Australia	2014	RCT	644	60-85	M&F	0.72
8	Goodall (2014)	Caneda	2014	RCT	600	18-20	M&F	0.54
9	Bergman (2015)	Sweden	2015	Cohort	124	All age	M&F	0.64
10	Martineau (2015)	England	2015	RCT	250	All age	M&F	0.99
11	Martineau (2015)	England	2015	RCT	240	All age	M&F	0.98
12	Martineau (2015)	England	2015	RCT	240	All age	M&F	0.96
13	Simpson (2015)	Australia	2015	Cohort	17	All age	M&F	0.98
14	Denlinger (2016)	America	2016	RCT	408	All age	M&F	0.97
15	Ginde (2017)	America	2017	RCT	107	>63	M&F	0.60
16	Shimizu (2018)	Japan	2018	RCT	428	All age	M&F	0.91
17	Slow (2018)	New zealand	2018	RCT	117	All age	M&F	0.95
18	Aloia (2019)	America	2019	RCT	260	All age	Female	0.96
19	Arihiro (2019)	Japan	2019	RCT	223	All age	M&F	0.59
20	Camargo (2020)	America	2020	RCT	5110	50-84	M&F	0.99

Table 2 The odds ratio of Respiraory tract infections in vitamin D users in different studies and determining the homogeneity of studies using a stochastic effect model

Study	Odds ratio	Asurnce distance 95%	Test statistics	P_value
Aloia (2007)	0.31	(0.36-0.26)	48.51	<0.001
Li-Ng (2009)	0.89	(0.93-0.83)		
Laaksi (2010)	0.76	(0.81-0.68)		

Murdoch (2012)	0.99	(0.99-0.97)		
De Gruijl (2012)	0.86	(0.91-0.78)		
Rees (2013)	0.93	(0.94-0.91)		
Tran (2014)	0.72	(0.75-0.68)		
Goodall (2014)	0.54	(0.58-0.5)		
Bergman (2015)	0.64	(0.72-0.55)		
Martineau (2015)	0.99	(0.997-0.966)		
Martineau (2015)	0.98	(0.992-0.952)		
Martineau (2015)	0.96	(0.979-0.926)		
Simpson (2015)	0.98	(0.999-0.622)		
Denlinger (2016)	0.97	(0.983-0.948)		
Ginde (2017)	0.6	(0.688-0.505)		
Shimizu (2018)	0.91	(0.934-0.879)		
Slow (2018)	0.95	(0.978-0.892)		
Aloia (2019)	0.96	(0.978-0.928)		
Arihiro (2019)	0.59	(0.653-0.524)		
Camargo (2020)	0.99	(0.992-0.987)		
Integrated total (random effects)	0.797	(0.808-0.786)		
Indiator I^2	98.86			

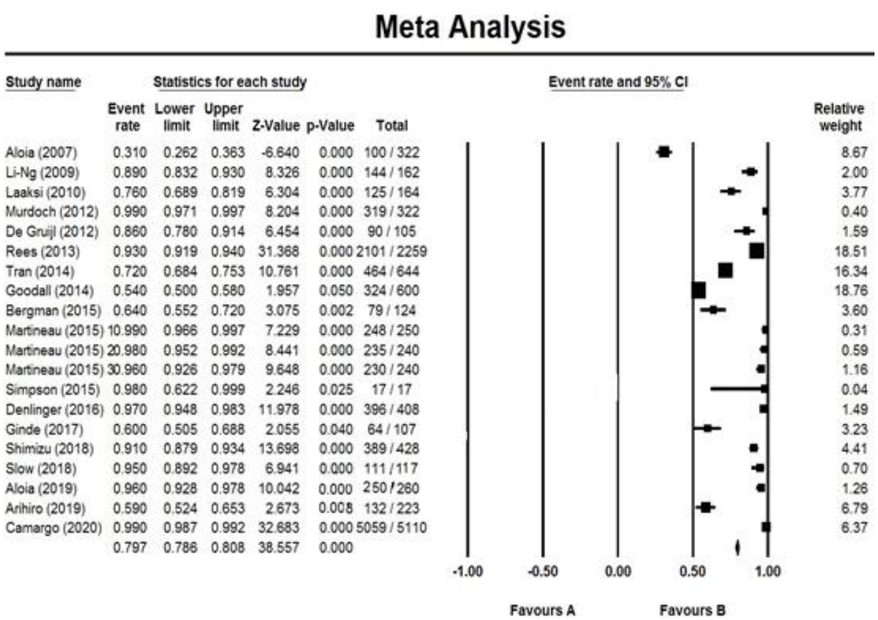

Figure 1 Forest plot chart the odds ratio of Resiraory tract infections in vtamin D users in different studies.

In a review of articles on the effect of vitamin C on respiratory infections, 2 case-control studies by Van Straten et al., (2002) in Japan with a odds ratio of respiratory infections in vitamin C users of 0.99 and Study by Sasazuki et al., (2006) in the United States with a odds ratio of respiratory infections in vitamin C users of 0.34 and 1 RCT study by Johnston et al., (2014) in Finland with a odds ratio of respiratory infections in Consumers of vitamin C 0.55. Therefore, the odds ratio of respiratory tract infections in consumers of vitamin C between 2000-2000, 0 .406 (95 confidence interval, 0.55-0.441) was estimated.

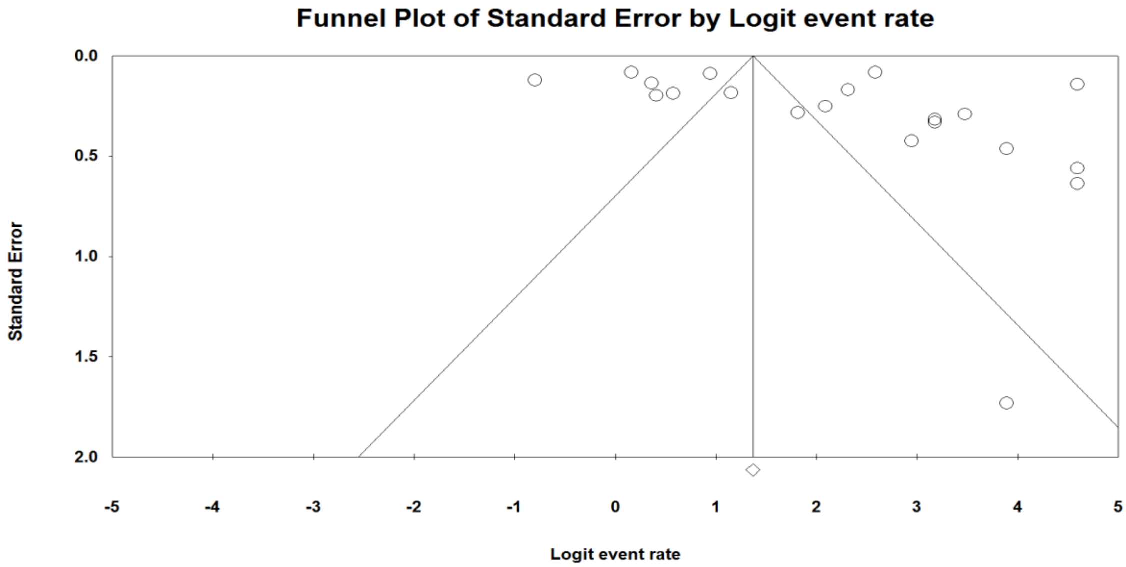

Figure 2 funnel plot chart for ipord studies

Table 3 Spefications of aticles on the role of zinc on respiratory infections

row	Author	Country	Year of publication	Type of study	Number of samples	Age	Sex	OR
1	Turner (2000)	America	2001	RCT	91	All age	M & F	0.99
2	Osendarp (2002)	Bangladesh	2002	RCT	91	0-2	Boy & girl	0.3
3	Veverka (2009)	America	2009	Cross-sectional	40	All age	M & F	0.99
4	Shah (2013)	Australia	2012	RCT	96	5-18	M & F	0.3
5	Martinez-Estevez (2016)	Columbia	2016	RCT	355	5-18	M & F	0.99

Table 4 the odds ratio of Resiraory tract infections in zinc users in different studies and determining the homogeneity of studies using a stochastic effect model

Study	Odds ratio (%)	Asurnce distance 95%	Test statistics	P_value
Turner (2000)	0.99	(0.999-0.926)	126.95	<0.001
Osendarp (2002)	0.3	(0.402-0.215)		
Veverka (2009)	0.99	(0.815-1)		
Shah (2013)	0.3	(0.399-0.217)		
Martinez-Estevez (2016)	0.99	(0.996-0.972)		
Integrated totl (random effects)	0.437	(0.51-0.366)		
Indicator I^2	96.84			

According to the results of the table 3 and 4, due to the heterogeneity of the studies and the significance of the heterogeneity index, the stochastic effects model was used in the meta-analysis. The heterogeneity of the stochastic effects model in this study was 96.84% (P> 0.05). Therefore, the odds ratio of respiratory infections in zinc users between 2020 and 2001, 0 .437 (95% confidence interval, 0.51 - 0.366) was estimated (Figures 3 and 4).

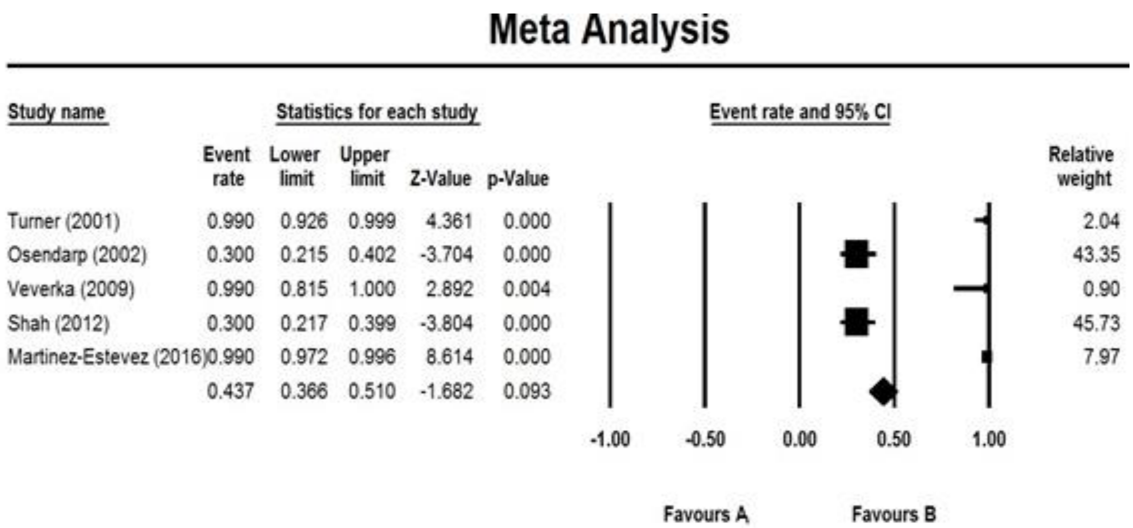

Figure 3 Forest plot chart the odds ratio of Resiraory tract infections in zinc users in different studies.

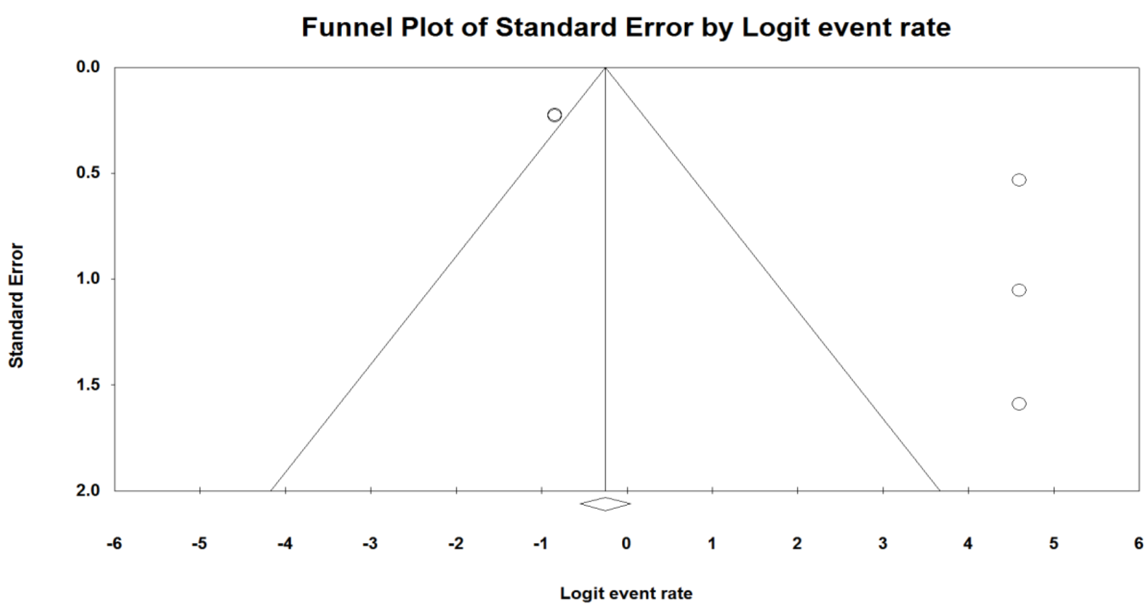

Figure 4 Funnel plot chart for imported studies

In a review of articles on the effects of selenium on respiratory infections, 1 cohort study by Raposo et al., (2017) in Sweden with an odds ratio of respiratory infections of selenium users of 0.78. Roudi et al., (2020) found that in the United States, the odds of selenium infections were found to be 0.2. Therefore, the odds ratio of respiratory infections in selenium users between 2000-2000, 0, 624 (95% confidence interval, 0.545 – 0.696) was estimated.

4. DISCUSSION

Based on the results of the current work, the odds ratio of respiratory tract infections in consumers of vitamin D 0.797 (Confidence interval 95%, 0.808-0.786) was estimated. The odds ratio of respiratory tract infections in consumers of vitamin C, 0.496 (95% confidence interval, 0.55-0.441) was estimated. Rate of odds of respiratory infections in zinc users, 0.437 (95% confidence interval, 0.51-0.366) was estimated. The odds ratio of respiratory infections in selenium users, 0.624 (Confidence interval 95%, 0.545 - 0.696) was estimated.

Vitamin C is one of the types of vitamins and micronutrients that can be used to promote the immune system and protect the respiratory system against inflammation. Vitamin C has a strong antioxidant effect. Therefore, in many situations where oxidative stress increases in the body, the antioxidant effect of this vitamin can be very important. Many infections increase the activity of phagocytes, increase free radical levels, and vitamin C protects host cells against free radicals released by phagocytes. In diseases such as the common cold and other infections, the amount of vitamin C in plasma, leukocytes and urine decreases. Numerous studies show that vitamin C is effective in preventing, shortening and improving many infections. Vitamin C strengthens the immune system and protects against many infections (Hemilä, 2017). This vitamin in immune system cells, improves chemotaxis, phagocytosis, and ultimately kills bacteria and viruses. A study in birds has shown that this vitamin increases the resistance of chickens' tracheal tissue to coronavirus infection in culture (Hemilä, 2003). This vitamin also has antihistamine function and relieves symptoms such as: runny nose, nasal congestion, swollen sinuses, itchy nose, etc. and in some cases has been found to prevent pneumonia. Some new diseases such as Covid-19, lower respiratory tract infections are common, so this vitamin is used as a possible option in the treatment of this disease: oranges, kiwis, tangerines, squash, tomatoes, strawberries, bell peppers, Cabbage and grapefruit are examples of rich sources of vitamin C.

Vitamin D is a fat-soluble vitamin. The main source of this vitamin is sunlight and is found naturally in plant and animal foods such as liver, fish, egg yolks, cod liver oil, tuna and dairy products, but in small amounts. Inadequate amounts and the prevalence of deficiency of this vitamin make it necessary to take supplements of this vitamin (Christakos et al., 2013). The effective form of vitamin D 1 and 25 dihydroxy is calciferol with calcitriol, which is formed by two hydroxylation reactions in the liver and kidneys. Vitamin D can reduce the risk of respiratory infections, especially viral ones (Nonnecke et al., 2014). Vitamin D deficiency in winter also leads to a viral epidemic. During the winter, people who do not take vitamin D supplements have lower serum concentrations of 25 hydroxy (Cannell et al., 2006). This vitamin, if it has higher concentrations of 25 hydroxy in the serum, can increase the risk of epidemics and viral pandemics, chronic diseases including cancer (McDonnell et al., 2016), cardiovascular disease (Gholami et al., 2019), chronic respiratory infections (Zhu et al., 2016). Reduce diabetes mellitus (Pittas et al., 2019) and hypertension (Manson et al., 2019). Vitamin D reduces respiratory tract infections with the help of three reactions: 1- Maintaining strong connections between cells (Schwalfenberg, 2011), 2- Killing viruses through cathelsidin and difensin (Liu et al., 2006) 3- Reducing the production of inflammatory cytokines that cause pneumonia Various studies have shown that high concentrations of 25 hydroxy in serum can reduce the risk of dengue fever (d), herpes virus (Farnoosh et al., 2020), hepatitis B and HIV (Arihiro et al., 2019) C (Gui et al., 2017), influenza (Currie et al., 2013), pneumonia and Be viral infections. Therefore, it can be said that this vitamin may be effective in the treatment and prevention of Covid-19 infection.

Selenium is a mineral that is important both in metabolism and in the activity of the oxidative-regenerative system. This mineral can prevent the formation of free radicals and oxidative damage to cells and tissues (Denlinger et al., 2016). Selenium deficiency causes health problems and affects both types of immune systems: cellular immunity and humoral immunity, and taking selenium supplements improve the strength of the immune system. Selenium deficiency can not only increase the risk of infection due to influenza virus, but also cause changes in the virus genome and thus increase the severity of the virus (Guillin et al., 2019; Beck et al., 1995; Brandão-Neto et al., 1995). So selenium deficiency, in addition to improving the function of the immune system also affects the virus.

Zinc is classified as an antioxidant, which is an essential structure of superoxide dismutase (SOD) and a co-factor in important enzymes in glucose and lipid metabolism, which prevents lipid peroxidation. It stabilizes the cell membrane and the presence of the right amount of zinc in the body reduces free radicals and the amount of inflammation, so it can be stated that there is an inverse relationship between zinc and inflammatory factors. The study found that the addition of zinc supplements or syrups containing Zinc in the medication regimen of children with zinc deficiency in their body reduces the mortality rate. According to studies, it can be said that zinc can reduce the symptoms of respiratory tract infections and inflammation in patients with Covid -19.

Among the diseases that cause infections in the respiratory system is Covid-19 is an contagious disease that can be transmitted from human to human and is classified as a coronavirus (Schoeman & Fielding, 2019; Cohen & Normile, 2020; Zhu et al., 2020; Li et al., 2020). In this infectious disease, each infected person can infect an average of 3 other people. According to various tests on Corona, the similarity of this newly known virus with SARS corona virus is more than 82%. Due to the lack of drug treatments and vaccines for the new viruses that exist today (such as the Covid-19 virus), there are methods such as supplementation and micronutrients that can help the immune system to prevent, control and replicate the spread of the virus is needed. Schoeman & Fielding, (2019) found that idiopathic pulmonary fibrosis is chronic respiratory diseases. One of the causes of its occurrence and exacerbation is imbalance in the antioxidant system and inflammation, and the study was performed with the aim of the effect of supplementation of these vitamins on lung function tests in adults with pulmonary fibrosis. The procedure of this quasi-experimental clinical trial was as follows: 33 patients with pulmonary fibrosis took vitamin C and D for 200 months in doses of 50,000 units of 250 mg and 200 units of dose, respectively. At the beginning and end of the study, seizure variables and body mass index, questionnaires of food intake, physical activity and sun exposure and respiratory were examined. Lung function factors were measured using spirometry and plethysmography.

Findings obtained from spirometry and plethysmography tests showed extraordinary increase in the percentage of forced expiratory volume in the first second P = 0.016, tail storage jam P = 0.001, residual volume P = 0.002 and total lung capacity P = 0.003. The variables of forced vital capacity, vital capacity, ratio of forced expiratory volume in the first second to forced vital valence and expiratory reservoir volume were not significantly different. Respiratory function score was significantly improved according to the St. George Questionnaire and no significant difference was observed in the confounding variables. It is concluded that the consumption of three vitamins C and DE had a significant effect on the respiratory function of patients (Banerjee et al., 2019) with the object of distinguish the effect of a course of aerobic exercise and vitamin D supplementation of 1000 units on respiratory indices and Performed asthma patients. This quasi-experimental study was performed on 32 women with asthma with an average age of 20 to 30 years. Samples in one of 4 groups of 8 people included: 1- AT + S group who had practice and vitamin D supplementation. 2- AT group who participated in sports exercises only 3- S group who took only vitamin D supplements. 4 - Group C, which had no exercise program and supplementation, were included. The results showed that the first two groups, namely AT + S and AT, had respiratory and performance improvements in respiratory indices. It was concluded that aerobic sport and vitamin D consumption for 8 weeks improves pulmonary function index and improves aerobic function in asthmatic patients, which can be part of their program (Farnoosh et al., 2020).

924 people with CF, roughly equal in sex, six months to 59 years of age, 16 placebo supplements (placebo), and four supplemental studies compared the inhaler with the placebo. According to their results, vitamin and mineral supplements do not appear to improve clinical outcomes the effect of antioxidants without a very large and lengthy study, and they suggested that further research should look at how the effect of antioxidants on people with CF receiving CFTR modulator therapies (Schoeman & Fielding, 2019). Zinc plays the role of messaging in modulating inflammatory responses (Maywald et al., 2017). Similarly, changes in zinc status significantly affect the body's immune response and thus increase susceptibility to inflammatory and infectious diseases such as Acquired Immune Deficiency Syndrome, Measles, Malaria, Tuberculosis, and Pneumonia (Gammoh & Rink, 2017).

Previous data show that the state of society is associated with the prevalence of respiratory infections in children and adults (Aftanas et al., 2011; Walker et al., 2013). Due to the highoutbreak of zinc leakage worldwide (up to 17%), its affects public health has been considered as a significant issue (Bailey et al., 2015). In addition, some of people, such as infants, especially premature infants, and the elderly, are at high risk for zinc deficiency and its adverse effects (Yasuda & Tsutsui, 2016). Coronaviridae is considered as the etiologic agent in 6-29% of respiratory infections (Berry et al., 2015; Peiris, 2016), although the intensity of the disease varies considerably with the type of virus and its virulence (Docea et al., 2020).

In particular, Zn2 + cations have been shown to inhibit the activity of SARS coronavirus RNA polymerase (RdRp, dependent RNA polymerase RNA), especially in combination with zinc ionophore pyrithione, by reducing its proliferation (Te Velthuis et al., 2010). These important findings suggest that Zn2 + may be considered as a specific antiviral agent in the treatment of 19 COVIDs. The number of samples studied in the above studies was much lower than the present study, so the presence of these factors may be one of the possible reasons for differences in the results of antibiotic resistance.

5. CONCLUSION

Ass results of the previous study and the present study, it seems, results of the studies as well as statistical indicators, a heterogeneity and fluctuation in the odds ratio of respiratory infections in consumers of vitamin D, vitamin C, Zinc and selenium are observed. Proper use of vitamin D, vitamin C, zinc and selenium is essential along with monitoring the epidemiology of regional respiratory infections.

Ethical Code

IR.ABADANUMS.REC.1399.170.

Funding

The study did not receive any external funding.

Conflict of interests

The authors declare that there are no conflicts of interests.

Data and materials availability

All data associated with this study are present in the paper.

REFERENCES AND NOTES

1. Abduljawad EA. Saudi society's dietary habits and the use of nutritional supplements during the corona pandemic: A cross-sectional retrospective study. Medical Science 2021;25(112):1248-1260
2. Aftanas LI, Berezkina ES, Bonitenko EY, Varenik VI, Grabeklis AR, Demidov VA, Kiselev MF, Nechiporenko SP, Nikolaev VA, Skalny AV, Skalnaya MG. Element status of population of Russia. Part II. Element status of population of Central Federal Region. Saint Petersburg: ELBI-SPb. 2011.
3. Alimohamadi Y, Sepandi M. Basic Reproduction Number: An important Indicator for the Future of the COVID-19 Epidemic in Iran. J Mil Med 2020; 22:96-7.
4. Aloia JF, Islam S, Mikhail M. Vitamin D and Acute Respiratory Infections—The PODA Trial. InOpen forum infectious diseases 2019 (Vol. 6, No. 9, p. ofz228). US: Oxford University Press.
5. Aloia JF, Li-Ng M. RE: epidemic influenza and vitamin D epidemiology and infection. Epidemiol Infect 2007; 135:1095-8.
6. Arihiro S, Nakashima A, Matsuoka M, Suto S, Uchiyama K, Kato T, Mitobe J, Komoike N, Itagaki M, Miyakawa Y, Koido S, Hokari A, Saruta M, Tajiri H, Matsuura T, Urashima M. Randomized Trial of Vitamin D Supplementation to Prevent Seasonal Influenza and Upper Respiratory Infection in Patients With Inflammatory Bowel Disease. Inflamm Bowel Dis 2019; 25(6):1088-1095.
7. Bailey RL, West Jr KP, Black RE. The epidemiology of global micronutrient deficiencies. Ann Nutr Metab 2015; 66:22-33.
8. Banerjee A, Kulcsar K, Misra V, Frieman M, Mossman K. Bats and coronaviruses. Viruses. 2019; 11:41.
9. Beck MA, Shi Q, Morris VC, Levander OA. Rapid genomic evolution of a non-virulent coxsackievirus B3 in selenium-deficient mice results in selection of identical virulent isolates. Nat Med 1995; 1:433-6.
10. Bergman P, Norlin AC, Hansen S, Björkhem-Bergman L. Vitamin D supplementation to patients with frequent respiratory tract infections: a post hoc analysis of a randomized and placebo-controlled trial. BMC Res Notes 2015; 8:391. doi: 10.1186/s13104-015-1378-3.
11. Berry M, Gamieldien J, Fielding BC. Identification of new respiratory viruses in the new millennium. Viruses 2015; 7:996-1019.
12. Brandão-Neto J, Stefan V, Mendonça BB, Bloise W, Castro AVB. The essential role of zinc in growth. Nutr Res 1995; 15:335-58.
13. Camargo CA, Sluyter J, Stewart AW, Khaw KT, Lawes CMM, Toop L, Waayer D, Scragg R. Effect of Monthly High-Dose Vitamin D Supplementation on Acute Respiratory Infections in Older Adults: A Randomized Controlled Trial. Clin Infect Dis 2020; 71(2):311-317. doi: 10.1093/cid/ciz801.
14. Cannell JJ, Vieth R, Umhau JC, Holick MF, Grant WB, Madronich S, Garland CF, Giovannucci E. Epidemic influenza and vitamin D. Epidemiol Infect 2006; 134(6):1129-40. doi: 10.1017/S0950268806007175.
15. Christakos S, Hewison M, Gardner DG, Wagner CL, Sergeev IN, Rutten E, Pittas AG, Boland R, Ferrucci L, Bikle DD. Vitamin D: beyond bone. Ann N Y Acad Sci 2013; 1287(1):45-58. doi: 10.1111/nyas.12129.
16. Cohen J, Normile D. New SARS-like virus in China triggers alarm. Am Assoc Adv Sci; 2020.
17. Currie SM, Findlay EG, McHugh BJ, Mackellar A, Man T, Macmillan D, Wang H, Fitch PM, Schwarze J, Davidson DJ. The human cathelicidin LL-37 has antiviral activity against respiratory syncytial virus. PLoS One 2013; 8(8):e73659. doi: 10.1371/journal.pone.0073659
18. De Gruijl FR, Pavel S. The effects of a mid-winter 8-week course of sub-sunburn sunbed exposures on tanning, vitamin D status and colds. Photochem Photobiol Sci 2012; 11:1848–54.
19. Denlinger LC, King TS, Cardet JC, Craig T, Holguin F, Jackson DJ, Kraft M, Peters SP, Ross K, Sumino K, Boushey HA, Jarjour NN, Wechsler ME, Wenzel SE, Castro M, Avila PC; NHLBI Asthma Net Investigators. Vitamin D Supplementation and the Risk of Colds in Patients with Asthma. Am J Respir Crit Care Med 2016; 193(6):634-41. doi: 10.1164/rccm.201506-1169OC.
20. Docea AO, Tsatsakis A, Albulescu D, Cristea O, Zlatian O, Vinceti M, Moschos SA, Tsoukalas D, Goumenou M, Drakoulis N, Josef M Dumanov, Victor A Tutelyan, Gennadii G Onischenko, Michael Aschner, Demetrios A Spandidos, Daniela Calina: A new threat from an old enemy: Re-emergence of coronavirus (Review). Int J Mol Med 2020; 45: 1631-1643.
21. Farnoosh G, Alishiri G, Hosseini Zijoud S R, Dorostkar R, Jalali Farahani A. Understanding the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and Coronavirus Disease (COVID19) Based on Available Evidence - A Narrative Review. J Mil Med 2020; 22:1-11.
22. Gammoh NZ, Rink L. Zinc in infection and inflammation. Nutrients 2017; 9:624.
23. Gholami F, Moradi G, Zareei B. The association between circulating 25-hydroxyvitamin D and cardiovascular diseases: a meta-analysis of prospective cohort studies. BMC Cardiovasc Disord 2019; 19: 248.

24. Ginde AA, Blatchford P, Breese K, Zarrabi L, Linnebur SA, Wallace JI, Schwartz RS. High-Dose Monthly Vitamin D for Prevention of Acute Respiratory Infection in Older Long-Term Care Residents: A Randomized Clinical Trial. J Am Geriatr Soc 2017; 65(3):496-503. doi: 10.1111/jgs.14679.
25. Goodall EC, Granados AC, Luinstra K, Pullenayegum E, Coleman BL, Loeb M, Smieja M. Vitamin D3 and gargling for the prevention of upper respiratory tract infections: a randomized controlled trial. BMC Infect Dis 2014; 14:273. doi: 10.1186/1471-2334-14-273.
26. Gui B, Chen Q, Hu C, Zhu C, He G. Effects of calcitriol (1, 25-dihydroxy-vitamin D3) on the inflammatory response induced by H9N2 influenza virus infection in human lung A549 epithelial cells and in mice. Virol J 2017; 14(1):10.
27. Guillin OM, Vindry C, Ohlmann T, Chavatte L. Selenium, selenoproteins and viral infection. Nutrients 2019; 11:2101.
28. Hemilä H. Vitamin C and Infections. Nutrients 2017; 9:339.
29. Hemilä H. Vitamin C and SARS coronavirus. J Antimicrob Chemother 2003; 52: 1049-50.
30. Johnston CS, Barkyoumb GM, Schumacher SS. Vitamin C supplementation slightly improves physical activity levels and reduces cold incidence in men with marginal vitamin C status: A randomized controlled trial. Nutrients 2014; 6:2572-83.
31. Laaksi I, Ruohola JP, Mattila V, Auvinen A, Ylikomi T, Pihlajamäki H. Vitamin D supplementation for the prevention of acute respiratory tract infection: a randomized, double-blinded trial among young Finnish men. J Infect Dis 2010; 202(5):809-14. doi: 10.1086/654881. PMID: 20632889.
32. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, Ren R, Leung k, Jessica Y. Wong, Xing X, Xiang N. Early transmission dynamics in Wuhan, China, of novel coronavirus–infected pneumonia. New Engl J Med 2020.
33. Li-Ng M, Aloia JF, Pollack S. A randomized controlled trial of vitamin D3 supplementation for the prevention of symptomatic upper respiratory tract infections. Epidemiol Infect 2009; 137:1396–404.
34. Liu PT, Stenger S, Li H, Wenzel L, Tan BH, Krutzik SR. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. Science 2006; 311:1770-3.
35. Manson JE, Cook NR, Lee I-M, Christen W, Bassuk SS, Mora S. Vitamin D supplements and prevention of cancer and cardiovascular disease. New Engl J Med 2019; 380:33-44.
36. Martineau AR, Hanifa Y, Witt KD. Double-Blind Randomized controlled trial of vitamin D3 supplementation for the prevention of acute respiratory infection in older adults and their carers (ViDiFlu). Thorax 2015; 70:953–60.
37. Martineau AR, James WY, Hooper RL. Vitamin D3 supplementation in patients with chronic obstructive pulmonary disease (ViDiCO): a multicentre, double-blind, Randomized controlled trial. Lancet Respir Med 2015; 3:120–30.
38. Martineau AR, MacLaughlin BD, Hooper RL. Double-Blind randomised placebo-controlled trial of bolus-dose vitamin D3 supplementation in adults with asthma (ViDiAs). Thorax 2015; 70:451–7.
39. Martinez-Estevez NS, Alvarez-Guevara AN, Rodriguez-Martinez CE. Effects of zinc supplementation in the prevention of respiratory tract infections and diarrheal disease in Colombian children: A 12-month randomised controlled trial. Allergol Immunopathol 2016; 44:368-75.
40. Maywald M, Wessels I, Rink L. Zinc signals and immunity. Int J Mol Sci 2017; 18:2222.
41. McDonnell SL, Baggerly C, French CB, Baggerly LL, Garland CF, Gorham ED, Lappe JM, Heaney RP. Serum 25-hydroxyvitamin D concentrations≥ 40 ng/ml are associated with> 65% lower cancer risk: pooled analysis of randomized trial and prospective cohort study. PloS one 2016; 11:e0152441.
42. Murdoch DR, Slow S, Chambers ST, Jennings LC, Stewart AW, Priest PC, Florkowski CM, Livesey JH, Camargo CA, Scragg R. Effect of vitamin D3 supplementation on upper respiratory tract infections in healthy adults: the VIDARIS randomized controlled trial. Jama 2012; 308:1333-9.
43. Nonnecke B, McGill J, Ridpath J, Sacco R, Lippolis J, Reinhardt T. Acute phase response elicited by experimental bovine diarrhea virus (BVDV) infection is associated with decreased vitamin D and E status of vitamin-replete preruminant calves. J Dairy Sci 2014; 97:5566-79.
44. Osendarp SJ, Santosham M, Black RE, Wahed MA, Van Raaij JM, Fuchs GJ. Effect of zinc supplementation between 1 and 6 mo of life on growth and morbidity of Bangladeshi infants in urban slums. Am J Clin Nutr 2002; 76:1401-8.
45. Pittas AG, Dawson-Hughes B, Sheehan P, Ware JH, Knowler WC, Aroda VR, Brodsky I, Ceglia L, Chadha C, Chatterjee R, Desouza C. Vitamin D supplementation and prevention of type 2 diabetes. New Engl J Med 2019; 381:520-30.
46. Raposo SE, Fondell E, Ström P, Bälter O, Bonn SE, Nyren O, Plymoth A, Bälter K. Intake of vitamin C, vitamin E, selenium, zinc and polyunsaturated fatty acids and upper respiratory tract infection—a prospective cohort study. Eur J Clin Nutr 2017; 71:450-7.
47. Rees JR, Hendricks K, Barry EL, Peacock JL, Mott LA, Sandler RS, Bresalier RS, Goodman M, Bostick RM, Baron JA. Vitamin D3 supplementation and upper respiratory tract infections in a randomized, controlled trial. Clin Infect Dis 2013; 57(10):1384-92. doi: 10.1093/cid/cit549.
48. Richman DD, Whitley RJ, Hayden FG, editors. Clinical virology. John Wiley & Sons; 2020.
49. Roudi F, Khademi G, Ranjbar G, Rafatpanah H, Esmaily H, Nematy M. Effects of High-Dose Selenium Supplementation

on Oxidative Stress and Inflammatory Markers in Critically Ill Children after Gastrointestinal Surgery: A Randomized Clinical Trial. Iran J Pediatr 2020; 30(4).

50. Sasazuki S, Sasaki S, Tsubono Y, Okubo S, Hayashi M, Tsugane S. Effect of vitamin C on common cold: randomized controlled trial. Eur J Clin Nutr 2006; 60:9-17.
51. Schoeman D, Fielding BC. Coronavirus envelope protein: current knowledge. Virol J 2019; 16:69.
52. Schwalfenberg GK. A review of the critical role of vitamin D in the functioning of the immune system and the clinical implications of vitamin D deficiency. Mol Nutr Food Res 2011; 55:96-108.
53. Shah UH, Abu-Shaheen AK, Malik MA, Alam S, Riaz M, Al-Tannir MA. The efficacy of zinc supplementation in young children with acute lower respiratory infections: a randomized double-blind controlled trial. Clin Nutr 2013; 32:193-9.
54. Shimizu Y, Ito Y, Yui K, Egawa K, Orimo H. Intake of 25-Hydroxyvitamin D3 Reduces Duration and Severity of Upper Respiratory Tract Infection: A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Comparison Study. J Nutr Health Aging 2018; 22(4):491-500. doi: 10.1007/s12603-017-0952-x.
55. Simpson S, van der Mei I, Stewart N, Blizzard L, Tettey P, Taylor B. Weekly cholecalciferol supplementation results in significant reductions in infection risk among the vitamin D deficient: results from the CIPRIS pilot RCT. BMC Nutr 2015; 1(1):1-0.
56. Slow S, Epton M, Storer M, Thiessen R, Lim S, Wong J, Chin P, Tovaranonte P, Pearson J, Chambers ST, Murdoch DR. Effect of adjunctive single high-dose vitamin D 3 on outcome of community-acquired pneumonia in hospitalised adults: The VIDCAPS randomised controlled trial. Sci Rep 2018; 8(1):1-9.
57. Te Velthuis AJ, van den Worm SH, Sims AC, Baric RS, Snijder EJ, van Hemert MJ. Zn2+ inhibits coronavirus and arterivirus RNA polymerase activity in vitro and zinc ionophores block the replication of these viruses in cell culture. PLoS Pathog 2010; 6:e1001176.
58. Tran B, Armstrong BK, Ebeling PR, English DR, Kimlin MG, van der Pols JC, Venn A, Gebski V, Whiteman DC, Webb PM, Neale RE. Effect of vitamin D supplementation on antibiotic use: a randomized controlled trial. Am J Clin Nutr 2014; 99(1):156-61. doi: 10.3945/ajcn.113.063271.
59. Turner RB, Cetnarowski WE. Effect of treatment with zinc gluconate or zinc acetate on experimental and natural colds. Clin Infect Dis. 2000; 31:1202-8.
60. Van Straten M, Josling P. Preventing the common cold with a vitamin C supplement: a double-blind, placebo-controlled survey. Adv Ther 2002; 19:151-9.
61. Veverka DV, Wilson C, Martinez MA, Wenger R, Tamosuinas A. Use of zinc supplements to reduce upper respiratory infections in United States Air Force Academy cadets. Complement Ther Clin Pract 2009; 15:91-5.
62. Walker CL, Rudan I, Liu L, Nair H, Theodoratou E, Bhutta ZA, O'Brien KL, Campbell H, Black RE. Global burden of childhood pneumonia and diarrhoea. Lancet 2013; 381:1405-16.
63. Yasuda H, Tsutsui T. Infants and elderlies are susceptible to zinc deficiency. Sci Rep 2016; 6:1-7.
64. Zhang N, Wang L, Deng X, Liang R, Su M, He C, Hu L, Su Y, Ren J, Yu F, Du L. Recent advances in the detection of respiratory virus infection in humans. J Med Virol 2020; 92:408-17.
65. Zhu M, Wang T, Wang C, Ji Y. The association between vitamin D and COPD risk, severity, and exacerbation: an updated systematic review and meta-analysis. Int J Chron Obstruct Pulmon Dis 2016; 11:2597.
66. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P. A novel coronavirus from patients with pneumonia in China, 2019. New Engl J Med 2020.