Effects of Vitamin D Intake on FEV1 and COPD Exacerbation: A Randomized Clinical Trial Study

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Abstract

Aim: This study aimed to evaluate the effects of vitamin D intake on COPD exacerbation and FEV1 in the patients with severe and very severe COPD.

Methods: This double blind placebo control randomized clinical trial study was done in the Ashayer university hospital in Khorramabad in 2012. Eighty patients with severe and very severe COPD were randomly selected from those who recourse to the internal medicine clinic of Ashayer hospital. They were randomly allocated to case and placebo group. The patients received routine treatment for COPD. Along with the routine treatment, placebo group received 100,000 IU of oral vitamin D per month, for 6 months. Data was analyzed using SPSS computer software, paired t-test, independent t-test, non parametric t-test and Pearson correlation coefficients.

Results: In each group, there were 44 patients. After the intervention, there were significant differences in FEV1 and the number of COPD exacerbation between the case and control group patients. Also, after the study, in the case group, FEV1 was increased and the number of COPD exacerbation was decreased significantly.

Conclusion: Vitamin D intake decreased COPD exacerbation and improved FEV1 in the patients with severe and very severe COPD. It is suggested that baseline serum vitamin D levels will recorded in similar studies and the effect of vitamin D intake will evaluated regarding the baseline serum vitamin D levels.

Keywords: COPD, Exacerbation, FEV1, Vitamin D

1. Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a chronic disease that causes persistent airflow obstruction. The airflow obstruction in this disease is generally progressive (MacNee et al., 2005). COPD has two clinical phases (stable phase and exacerbation phase), both of which are associated with inflammation (Barbu et al., 2011). Smoking, passive smoking, reactivity of airways, occupational factors and air pollution are the risk factors of COPD (Reilly et al., 2004). Independent risk factors for COPD are male gender, advanced age, low socioeconomic status, occupational exposure and cigarette smoking (Caballero et al., 2008).

Based on the World Health Organization estimation, COPD will be the third cause of mortality in the world in 2020 (Murray et al., 1997). Ninety percent of COPD deaths occur in low and middle income countries (Murray et al., 1997). In European countries, depending on the age of participants, the methods used and the location, the prevalence of COPD ranged from 2.1% to 26.1% (Atsou et al., 2011). It was 8.9% in India (from 6.2% to 13.5%; based on spirometry) (Afonso et al., 2011), 3.02% in the Netherlands (in a population-based study including subjects ≥ 40) (8), 17.4% in Copenhagen (aged 35 years or older) (Fabricius et al., 2011) and 3.7% in Abu Dhabi (in 40-80 year old subjects) (Al Zaabi et al., 2011).

Nowadays, the attention to nonskeletal effects of vitamin D has been increased (Kunisaki et al., 2011). An association between pulmonary function and serum vitamin D levels has been reported in some studies. It has been reported that vitamin D deficiency correlates with severity of COPD (Janssens et al., 2010). Also, in some studies, it has been declared that COPD patients had a raised risk for vitamin D deficiency (Persson et al., 2012, Zhang et al., 2012). Likewise, in one study, it has been stated that total vitamin D intake was negatively associated with COPD (Shaheen et al., 2011).
According to previous studies, the effect of levels vitamin D is controversial on COPD exacerbation and FEV1. This study aimed to evaluate the effect of vitamin D intake on COPD exacerbation and FEV1 in the patients with severe and very severe COPD.

2. Method

This double-blind, placebo-controlled, randomized clinical trial was done in Ashayer university hospital in Khorramabad in 2012. The Ethics and Research Committee of Lorestan University of Medical Sciences approved this study. Furthermore, we obtained signed informed consents from all the participants. This study has been recorded in Iranian Registry of Clinical Trials at www.irct.ir as a clinical trial (IRCT2012071810332N1). Eighty-eight patients with severe and very severe COPD were randomly selected from those who recoursed to the internal medicine clinic of Ashayer hospital. Severe and very severe COPD were defined as Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines (Donaldson et al., 2002). The selected patients were allocated to the study and placebo groups by simple random sampling method. The patients in both the groups received the routine treatment for COPD. Along with the routine treatment, the study group received 100,000 IU of oral vitamin D per month, for 6 months. In contrast, the placebo group received oral placebo for 6 months. Before the study, forced expiratory volume in 1 second (FEV1) was determined, and the number of COPD exacerbations during the last 6 months was recorded in the both groups. After 6 months of treatment, FEV1 was determined, and the number of COPD exacerbations during the study span was evaluated in the both groups. The patients received a telephone call every 2 months to assess respiratory symptoms consistent with a COPD exacerbation. The definition of COPD exacerbation was either the presence of 2 or more of these major symptoms (increase in sputum purulence, sputum volume or dyspnea) or any of major symptoms accompanied by any of minor symptoms (increase in nasal discharge, wheeze, sore throat, cough or fever) for at least two consecutive days (Donaldson et al., 2002).

2.1 Statistics

The data was analyzed using the SPSS computer software and paired t-test, independent t-test, non-parametric t-test and Pearson correlation coefficients. The P-values<0.05 were considered statistically significant.

3. Results

In each group, there were 44 patients, 30 of whom (68.2%) were male. There were no significant differences between age distribution, cigarette smoking and addiction in the study and placebo groups (Table 1).

Table 1. Age distribution, cigarette smoking and addiction in case and placebo groups

|                        | Case group | Placebo group | p value |
|------------------------|------------|---------------|---------|
| **Age** (<45)          | 2 (4.5%)   | 1 (2.3%)      | 0.83    |
| (Year)                 |            |               |         |
| 45-60                  | 15 (34.1%) | 16 (36.4%)    |         |
| >60                    | 27 (61.4%) | 27 (61.4%)    |         |
| **Cigarette smoking**  |            |               |         |
| (cigarette per month)  |            |               |         |
| None                   | 11 (25%)   | 13 (29.5%)    | 0.22    |
| < 50                   | 26 (59.1%) | 23 (52.3%)    |         |
| > 50                   | 7 (15.9%)  | 6 (13.6%)     |         |
| **Addiction**          |            |               |         |
| None                   | 17 (38.6%) | 18 (40.9%)    | 0.53    |
| Oral use               | 9 (20.4%)  | 8 (18.2%)     |         |
| Inhalation use         | 16 (36.4%) | 18 (40.9%)    |         |
| Injection use          | 2 (4.5%)   | 0             |         |

The mean of FEV1 and COPD exacerbations according to sex, age distribution, cigarette smoking and addiction, before and after the study, are shown in Table 2 and Table 3.
Before the study, there were no significant differences in FEV1 and the number of COPD exacerbations between

### Table 2. The mean of FEV1 according to sex, age distribution, cigarette smoking and addiction, before and after the study

| Case | placebo |
|------|---------|
| Before | After | p value | Before | After | p value |
| Sex | Male | 33.6±7.7 | 51.2±5.9 | 0.0001 | 33.6±4.6 | 33.1±9.7 | 0.44 |
| | Female | 36.8±10 | 52.5±14.6 | 0.009 | 35.8±6.6 | 34.2±4.6 | 0.32 |
| p value | 0.3 | 0.76 | - | 0.17 | 0.59 | - |
| Age (Year) | <45 | 39±1.4 | 55±4.2 | - | 35±0 | 32 | - |
| | 45-60 | 36.8±8 | 51±13.9 | 0.004 | 35.6±9.4 | 34.2±8.4 | 0.062 |
| | >60 | 33.1±8.9 | 51.7±6.4 | 0.0001 | 34.5±9.2 | 34.8±7.7 | 0.13 |
| p value | 0.3 | 0.85 | - | 0.88 | 0.53 | - |
| Cigarettesmoking (cigarette/month) | None | 35.2±8.4 | 49.3±15.6 | 0.047 | 38.7±9.3 | 34.1±6.7 | 0.018 |
| | < 50 | 39.5±3.6 | 55.7±5.1 | <0.0001 | 38.7±4.4 | 35.7±5.4 | 0.011 |
| | > 50 | 33.07±9.1 | 51.5±6.4 | <0.0001 | 32.1±9.2 | 31.1±8.7 | 0.32 |
| p value | 0.19 | 0.38 | - | 0.063 | 0.31 | - |
| Addiction | None | 37±8.6 | 51.1±13.3 | 0.003 | 38.3±6.2 | 34.4±6.1 | 0.001 |
| | Oral use | 37.1±7.6 | 54.6±5.1 | <0.0001 | 36.1±11.7 | 30±9.2 | 0.015 |
| | Inhalation use | 32.1±7.8 | 51.6±6.7 | <0.0001 | 32.6±9.7 | 30.2±8 | 0.078 |
| | Injection use | 34±9.8 | 42.5±3.5 | - | - | - | - |
| p value | 0.187 | 0.42 | - | 0.164 | 0.23 | - |

### Table 3. The mean of COPD exacerbation according to sex, age distribution, cigarette smoking and addiction, before and after the study

| Case | Control |
|------|---------|
| Before | After | p value | Before | After | p value |
| Sex | Male | 18.8±3.5 | 9.8±1.3 | 0.0001 | 19.3±4.2 | 19.6±3.9 | 0.056 |
| | Female | 16.3±2.4 | 9.3±1.3 | 0.0023 | 18.1±2.5 | 17.7±2.5 | 0.73 |
| p value | 0.095 | 0.25 | - | 0.23 | 0.053 | - |
| Age (Year) | <45 | 19±1.4 | 10 | - | 18±0 | 18 | - |
| | 45-60 | 16.8±3.3 | 9.5±1.1 | 0.0001 | 18.8±1.4 | 17.8±1.6 | 0.79 |
| | >60 | 18.2±2.8 | 9.7±1.5 | <0.0001 | 19.4±2.9 | 19.7±2.9 | 0.64 |
| p value | 0.28 | 0.82 | - | 0.66 | 0.069 | - |
| Cigarette smoking (cigarette/month) | None | 17.1±1.9 | 8.8±1.3 | <0.0001 | 17.3±2.6 | 17.1±2.3 | 0.65 |
| | < 50 | 18.5±2.2 | 9.8±1.4 | <0.0001 | 19.2±3.3 | 19.2±2.8 | 0.38 |
| | > 50 | 19.1±3.4 | 10±1.2 | <0.0001 | 19.1±4.4 | 19.4±4.1 | 0.89 |
| p value | 0.185 | 0.038 | - | 0.42 | 0.2 | - |
| Addiction | None | 16.1±2.8 | 9.2±1.2 | <0.0001 | 17.5±3.1 | 17.8±3.5 | 0.42 |
| | Oral use | 20.4±4.7 | 10±1.8 | <0.0001 | 20±3.7 | 20.2±3.9 | 0.56 |
| | Inhalation use | 18.9±1.7 | 10±1.1 | <0.0001 | 19.2±4.4 | 19.2±3.4 | 0.99 |
| | Injection use | 15±2.1 | 10±1.4 | - | - | - | - |
| p value | 0.023 | 0.35 | - | 0.24 | 0.24 | - |
the study and placebo group patients. But, after the study, there were significant differences in FEV1 and the number of COPD exacerbations between the study and placebo group patients. Also, after the study, in the study group, FEV1 was increased and the number of COPD exacerbations was decreased significantly (Table 4).

Table 4. FEV1 and the number of COPD exacerbation in the case and placebo groups

|                      | Case       | Control    | p value |
|----------------------|------------|------------|---------|
| **FEV1**             |            |            |         |
| (M±SD) Before        | 34.6±8.5   | 34.4±9.2   | 0.89    |
| After                | 51.6±9.4   | 31.9±7.6   | <0.001  |
| **p value**          | <0.001     | 0.53       | -       |
| **COPD exacerbation**|            |            |         |
| (M±SD) Before        | 18.02±3.3  | 18.7±3.8   | 0.38    |
| After                | 9.7±1.3    | 18.8±3.6   | <0.001  |
| **p value**          | <0.001     | 0.83       | -       |

4. Discussion

COPD is a chronic and common disease. COPD can cause severe complications. Afonso et al., reported that 26% and 2.8% of the patients with very severe COPD and non-COPD patients had died after 1 year of follow-up in the Netherlands (Afonso et al., 2011).

An association between pulmonary function and serum vitamin D levels has been reported in some studies. It has been reported that vitamin D deficiency correlates with the severity of COPD (Janssens et al., 2010). Also, it has been reported that a significant relation between FEV1 and serum 25-hydroxy vitamin D levels (Azargoon et al., 2011). However, in a study, baseline 25-hydroxy vitamin D levels were not predictive of acute exacerbation in patients with severe COPD (Kunisaki et al., 2012). But the relationship between vitamin D and COPD has been reported in some studies. Also, it has been stated that total vitamin D intake was negatively associated with COPD (Shaheen et al., 2011). Regarding these results, vitamin D intake can be beneficial in COPD patients. This study aimed to evaluate the effect of vitamin D intake on COPD exacerbation and FEV1 in the patients with severe and very severe COPD. According to our knowledge, the effect of vitamin D on FEV1 and COPD exacerbations has been studied in few studies.

In this study, vitamin D intake improved COPD exacerbations and FEV1 in the patients with severe and very severe COPD. Hornikx et al., reported that 100,000 IU of vitamin D per month for one year had improved maximal oxygen uptake and inspiratory muscle strength significantly in the COPD subjects who had followed a rehabilitation program (Hornikx et al., 2012). These findings can vindicate the results of our study.

In a similar study, Lehouck et al., compared the effects of vitamin D and placebo on FEV1 and exacerbation rate in the patients with moderate to very severe COPD (Lehouck et al., 2012). In their study, each patient received 100,000 IU of vitamin D every 4 weeks for 1 year. In contrast to our results, they reported that this dose of vitamin D had not improved FEV1 and exacerbation rate. This difference may be due to the difference between baseline serum vitamin D levels in these studies. Although serum vitamin D level was not determined in our study, some studies have stated that vitamin D deficiency is prevalent in Iran. Studies suggest that Vitamin D increase production IL-10, an antiinflammatory cytokine involved in the pathogenesis of asthma, from T cells, increase production IL-37, antimicrobial peptide, regulate matrix metalloproteinases (MMP), shifting theTh1 and Th2 balance and reducing inflammation (Xystrakis et al., 2006, De Smet et al., 2005; Finklea et al., 2011). Taken together vitamin D intake (100,000 IU per 4 weeks for 6 months) improved COPD exacerbation and FEV1 in the patients with severe and very severe COPD significantly. It is suggested that baseline serum vitamin D levels be recorded in similar studies and the effect of vitamin D intake be evaluated regarding the baseline serum vitamin D levels.

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References

Afonso, A. S., Verhamme, K. M. Sturkenboom, M. C., & Brusselle, G. G. (2011). COPD in the general population: Prevalence, incidence and survival. *Respir Med, 105*(12), 1872-1884.
Al Zaabi, A., Asad, F., & Abdou, J. (2011). Prevalence of COPD in Abu Dhabi, United Arab Emirates. *Respir Med, 105*(4), 566-570. http://dx.doi.org/10.1016/j.rmed.2010.12.008

Atsou, K., Chouaid, C., & Hejblum, G. (2011). Variability of the chronic obstructive pulmonary disease key epidemiological data in Europe: systematic review. *BMC Med, 18*(9), 7.

Azargoon, A. R., Moghadam, P. K., Shokrollahi, S., Ebrahimzadeh, F., & Pournia, Y. (2011). Relationship between FEV1 and 25-hydroxy Vitamin D in Patients with Chronic Obstructive Pulmonary Disease. *Trends in Medical Research, 6*, 184-190. http://dx.doi.org/10.3923/tmr.2011.184.190

Barbu, C., Iordache, M., & Man, M. G. (2011). Inflammation in COPD: pathogenesis, local and systemic effects. *Rom J Morphol Embryol, 52*(1), 21-27.

Caballero, A. Torres-Duque, C. A., & Jaramillo, C. (2008). Prevalence of COPD in five Colombian cities situated at low, medium, and high altitude. *Chest, 133*(2), 343-349. http://dx.doi.org/10.1378/chest.07-1361

De Smet, K., & Contreras, R. (2005). Human antimicrobial peptides: defensins, cathelicidins and histatins. *Biotechnol Lett, 27*, 1337-1347. http://dx.doi.org/10.1007/s10529-005-0936-5

Donaldson, G. C., Seemungal, T. A., Bhowmik, A., & Wedzicha, J. A. (2002). Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax, 57*(10), 847-852. http://dx.doi.org/10.1136/thx.57.10.847.

Fabricius, P., Løkke, A., Marott, J. L., Vestbo, J., & Lange, P. (2011). Prevalence of COPD in Copenhagen. *Respir Med, 105*(3), 410-417. http://dx.doi.org/10.1016/j.rmed.2010.09.019

Finklea, J. D., Grossmann, R. E., & Tangpricha, V. (2011). Vitamin D and Chronic Lung Disease: A Review of Molecular Mechanisms and Clinical Studies. *American Society for Nutrition. Adv. Nutr, 2*, 244-253. http://dx.doi.org/10.3945/an.111.000398

Hornikx, M., Van Remoortel, H., & Lehouck, A. (2012). Vitamin D supplementation during rehabilitation in COPD: A secondary analysis of a randomized trial. *Respir Res, 13*, 84. http://dx.doi.org/10.1186/1465-9921-13-8

Janssens, W., Bouillon, R., & Claes, B. (2010). Vitamin D deficiency is highly prevalent in COPD and correlates with variants in the vitamin D-binding gene. *Thorax, 65*(3), 215-220. http://dx.doi.org/10.1136/thx.2009.120659.

Kunisaki, K. M., Niewoehner, D. E., & Connett, J. E. (2012) COPD Clinical Research Network. Vitamin D levels and risk of acute exacerbations of chronic obstructive pulmonary disease: a prospective cohort study. *Am J Respir Crit Care Med, 185*(3), 286-290. http://dx.doi.org/10.1164/rccm.201109-1644OC.

Kunisaki, K. M., & Rector, T. S. (2011). Vitamin D and responses to inhaled fluticasone in severe chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis, 7*(6), 29-34. http://dx.doi.org/10.2147/COPD.S15358

Lehouck, A., Mathieu, C., & Carremans, C. (2012). High doses of vitamin D to reduce exacerbations in chronic obstructive pulmonary disease: a randomized trial. *Ann Intern Med, 156*(2), 105-114. http://dx.doi.org/10.7326/0003-4819-156-2-201201170-00004

MacNee, W., ZuWallack, R. L., & Keenan, J. (2005). *Clinical management of chronic obstructive pulmonary disease* (2nd ed.). Professional Communications, New York.

Murray, C. J., & Lopez, A. D. (1997). Global mortality, disability and the contribution of risk factors: Global burden of disease study. *Lancet, 349*, 1436-1442. http://dx.doi.org/10.1016/S0140-6736(96)07495-8.

Persson, L. J., Aanerud, M., Hiemstra, P. S., Hardie, J. A., Bakke, P. S., & Eagan, T. M. (2012). Chronic obstructive pulmonary disease is associated with low levels of vitamin D. *PLoS One, 7*(6), e38934. http://dx.doi.org/10.1371/journal.pone.0038934.

Reilly, J. J., Silverman, E. K., & Shapiro, S. D. (2004). *Harrison’s principles of internal medicine* (16th edition, 1547-1560). Chronic obstructive pulmonary disease. In: D. L. Kasper, E. Braunwald, A. S. Fauci, S. L. Hauser, D. L. Longo, & J. L. Jameson (Eds.), McGraw–Hill Professional.

Shaheen, S. O., Jameson, K. A., & Robinson, S. M. (2011). Relationship of vitamin D status to adult lung function and COPD. *Thorax, 66*(8), 692-698. http://dx.doi.org/10.1136/thx.2010.155234.

Xystrakis, E., Kusumakar, S., Boswell, S., Peek, E., Urry, Z., Richards, D. F., & Dallman, M. (2006). Reversing
the defective induction of IL-10-secreting regulatory T cells in glucocorticoid-resistant asthma patients. *J Clin Invest, 116*, 146-155. http://dx.doi.org/10.1172/JCI21759

Zhang, P., Luo, H., & Zhu, Y. (2012). Prevalence of vitamin D deficiency and impact on quality of life in patients with chronic obstructive pulmonary disease. *Journal of Central South University. Medical Sciences, 37*(8), 802-806. http://dx.doi.org/10.3969/j.issn.1672-7347.2012.08.008

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