Role of Vitamin D in Bronchiectasis (CF versus non CF patients)

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Abstract: Background: Bronchiectasis is a disease characterized by irreversible abnormal dilatation of bronchial tree**.** It may result from multiple etiologies most commonly infections, congenital or genetic disorders or idiopathic. Cystic fibrosis (CF) is the most common lethal autosomal recessive respiratory disease in the western world with an estimated incidence of 1 per 300 live births. Most patients with CF succumb to respiratory failure from chronic pulmonary failure infections. Vitamin D deficiency occurs frequently in patients with cystic fibrosis (CF) & non CF bronchiectasis. Vitamin D is important for optimal mineralization of bone. Vitamin D deficiency in these patients can arise from various causes including pancreatic exocrine insufficiency, lack of outdoor activity, and alterations of vitamin D metabolism. **Objectives:** To assess vitamin D level and determine its effect on pulmonary exacerbations in cystic fibrosis and non-cystic fibrosis bronchiectasis. **Patients and Methods:** Clinical trial. Chest department & chest clinic in El demerdash children hospital. This study included 40 patients (20 cystic fibrosis patients, 20 non cystic fibrosis bronchiectasis patients), 20 controls. Patients were recruited from the chest clinic of the children's Hospital, Ain Shams university hospitals. Vitamin D serum level was measured in CF & non CF bronchiectasis patients and controls & pulmonary function tests was done to all the patients prior starting vitamin D supplementation then vitamin D serum level was followed up in the patients after treatment & also pulmonary function tests were repeated. Controls were assessed by basal serum vitamin D level. **Results:** We found that mean age for bronchiectasis group 9.35±4.49 while mean age for cystic fibrosis patients5.35 ±4.02, we detected male predominance in cystic fibrosis patients (75%) while in non-CF bronchiectasis male predominance is 55% also we found that 67.5% of our patients were from consanguineous parents, consanguineous marriage is more prevalent in CF more than non CF patients as. 75% of CF patients had consanguineous parents (15 cases), while 60% of non CF bronchiectasis cases had consanguineous parents (12 cases). A large number of patients (18 patients) had positive family history of same condition (45% of cases). family history is more prevalent in cystic fibrosis patients than non CF bronchiectasis patients. 6o% of CF patients (12 cases) had family history & history of sib death with same condition, while only 30% of non CF bronchiectasis patients had positive family history of same condition. In our study it was found that vitamin D deficiency was prevalent more among cystic fibrosis patients then non cystic fibrosis bronchiectasis patients then in controls (75%, 45% & 10% respectively) with high significance statistically, while vitamin D insufficiency was prevalent more in non CF patients then CF patients then controls (40%, 20% & 15% respectively), and vitamin D sufficient levels detected more in control group then bronchiectasis group then CF patients (75%, 15% & 5% respectively). We found also that there is highly significant change in severity of exacerbation in both groups after vitamin D supplementation, % of improvement in severity of exacerbation is more in non-cystic fibrosis bronchiectasis than in cystic fibrosis bronchiectasis. that degree of improvement in FEV1 in group A (non CF bronchiectasis) improved by 16 % & in group B by 15% which is highly significant statistically & that degree of improvement in FVC in group A (non CF bronchiectasis) improved by 11 % & in group B by 14% which is highly significant statistically & that degree of improvement in FEV1/FVC in group A (non CF bronchiectasis) improved by 8 % & in group B by 13% which is highly significant statistically. **Conclusion:** There is an association between vitamin D deficiency and bronchiectasis (both CF & non-CF). It was found that bronchiectasis patients are more vitamin D deficient than normal population. The more deficiency in Vitamin D, the more sever the lung disease. Vitamin D deficiency is also associated with more risk for pulmonary exacerbations (IV antibiotics need, hospital stay, ICU admission and missed school days). Improving vitamin D status in bronchiectasis patients leads to improvement of pulmonary functions, less frequent & less sever exacerbations & hospital stay.

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Keywords: Vitamin D, Bronchiectasis, CF and non CF patients

1. Introduction

Bronchiectasis is a disease characterized by irreversible abnormal dilatation of bronchial tree**.** It may result from multiple etiologies most commonly infections, congenital or genetic disorders or idiopathic. Cystic fibrosis (CF) is the most common lethal autosomal recessive respiratory disease in the western world with an estimated incidence of 1 per 300 live births. Most patients with CF succumb to respiratory failure from chronic pulmonary failure infections **(Eastham et al., 2014).**

CF is caused by dysfunction of the CF transmembrane conductance regulator (CFTR) protein, a chloride channel present on epithelial cells. Thus, CFTR mutations affect the respiratory, gastrointestinal, hepatobiliary, and reproductive systems as well as sweat glands.

Vitamin D deficiency in patients with CF can arise from various causes including pancreatic exocrine Insufficiency, lack of outdoor activity and alterations of vitamin D metabolism **(Collawn & Matalon, 2014).**

Due to fat malabsorption resulting from pancreatic insufficiency, higher oral dose of vitamin D are necessary to correct and maintain optimal vitamin D status in patients with CF **(Salvatore et al., 2012)**

Non-cystic fibrosis (non-CF) bronchiectasis often start in childhood with a significant impact on adult morbidity. Bronchiectasis is conventionally used as a descriptive term for an irreversible pathological state characterized by chronic suppurative airway disease manifested clinically by chronic productive cough and radiologically by bronchial dilation and often thick-walled bronchi. Vitamin D deficiency occurs frequently in patients with cystic fibrosis (CF) & non CF bronchiectasis. Vitamin D is important for optimal mineralization of bone. Vitamin D deficiency in these patients can arise from various causes including pancreatic exocrine insufficiency, lack of outdoor activity, and alterations of vitamin D metabolism **(Vanstone et al., 2015).**

The mechanisms by which vitamin D may exert its beneficial actions in chronic lung diseases are likely related to the role vitamin D in modulating the adaptive and innate immune response. Higher vitamin D status is associated with better lung function and that vitamin D therapy may help recovery from pulmonary exacerbations of bronchiectasis in both CF & non-CF patients **(Cutting et al., 2015).**

The potential mechanisms by which vitamin D may preserve lung function based on studies in cystic fibrosis and other chronic lung disease include improved airway remodeling in response to injury, decreased airway inflammation, and decreased airway bacterial colonization. Vitamin D has been established to enhance the innate immune system by up-regulating antimicrobial peptides such as human cathelicidin (hCAP18 or its cleaved protein LL-37) **(Paccou et al., 2010).**

Vitamin D deficiency leads to more sever pulmonary exacerbation in both CF & non CF patients & improving vitamin D status leads to improvement of pulmonary fuctions and less frequent & less severe exacerbations. **(Eastham et al., 2014).**

Aim of the Work

To assess vitamin D level and determine its effect on pulmonary exacerbations in cystic fibrosis and non-cystic fibrosis bronchiectasis.

2. Patients and Methods

- **Type of study:**

Clinical trial

- **Study setting:**

Chest department & chest clinic in Eldemerdash children hospital.

- **Patients:**

This study included 20 cystic fibrosis patients, 20 non cystic fibrosis bronchiectasis patients, 20 controls (all should be above 6 months old).

Patients were recruited chest clinics of the children's Hospital, Ain Shams university hospitals.

Inclusion criteria:

- Age more than 6 months
- CF patients diagnosed positive sweat chloride test twice & or gene study.
- Patients with non CF bronchiectasis diagnosed clinically and radiologically (sweat chloride test negative).

Exclusion criteria:

- Age less than 6 months old
- Patients having other known chronic lung diseases.
- Patients with chromosomal disorders as Down syndrome.

Methods:

All patients will be evaluated by the followings:

- History, clinical symptoms & diagnosis.
- Weight, height, body mass index.
- Sweat chloride test result
- Radiological investigations (HRCT_chest, ECHO).
- Sputum culture.
- Vitamin D level prior & after start of supplementation.
- Pulmonary function test prior & after supplementation.

Vitamin D level prior & after start of supplementation

Assay of Serum Vitamin D

Blood samples:

Three ml of venous blood were collected from each child under aseptic conditions. Serum was separated and analyzed for vitamin D.

Test principle:

Human25_dihydroxy vitamin D (25-OH-D) ELISA Kit: *

Human 25-OH-D level in sample was assayed using purified human Hu 25OH-D antibody to coat microtiter plate wells, maked solid-phase antibody, then added 25-OH-D to wells, combined 25-OH-D antibody which with HRP labeled, become antibody – antigen-enzyme-antibody complex, after washing completely, added TMB substrate solution, TMB substrate become blue color At HRP enzyme-catalyzed, reaction is terminated by the addition of a sulphuric acid solution and the color change is measured spectrophotometric ally at a wavelength of 450nm.

Interpretation of the test:

The concentration of 25-OH-D in the samples is then determined by comparing the O.D. of the sample to the standard curve.

Currently accepted standards for defining vitamin D status in children and adolescents are:

- Vitamin D sufficiency: 25(OH)D ≥30 ng/mL
- Vitamin D insufficiency: 25(OH)D between 21 and 29ng/mL
- Vitamin D deficiency: 25(OH)D ≤20ng/ml.

Statistical analysis

Data were statistically described in terms of mean ± standard deviation (± SD), and range, or frequencies (number of cases) and percentages when appropriate. Correlation between various variables was done using Pearson moment correlation equation for linear relation in normally distributed variables. p values less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

3. Results

Table (1) shows that mean age for bronchiectasis group 9.35±4.49 while mean age for cystic fibrosis patients5.35 ±4.02, we detected male predominance in cystic fibrosis patients (75%) while in non-CF bronchiectasis male predominance is 55% also we found that 67.5% of our patients were from consanguineous parents, consanguineous marriage is more prevalent in CF more than non CF patients as. 75% of CF patients had consanguineous parents (15 cases), while 60% of non CF bronchiectasis cases had consanguineous parents (12 cases). A large number of patients (18 patients) had positive family history of same condition (45% of cases). family history is more prevalent in cystic fibrosis patients than non CF bronchiectasis patients. 6o% of CF patients (12 cases) had family history & history of sib death with same condition, while only 30% of non-CF bronchiectasis patients had positive family history of same condition.

Table (1) Demographic Data of studied subjects:

Group A non CF bronchiectasis Group B CF patients Group C controls		**Group A**	**Group B**	**Group C**	**Test value**	**P-value**	**Sig.**
		No. = 20	**No. = 20**	**No. = 20**			
Sex	Male	11 (55.0%)	15 (75.0%)	9 (45.0%)	3.840*	0.147	NS
	Female	9 (45.0%)	5 (25.0%)	11 (55.0%)			
Age (years)	Mean± SD	9.35 ± 4.49	5.35 ± 4.02	7.80 ± 4.32	4.440•	0.016	S
	Range	3 – 17	1 – 15	2 – 16			
Consanguinity	Positive	12 (60.0%)	15 (75.0%)	3 (15.0%)	3.239*	0.197	NS
	Negative	8 (40.0%)	5 (25.0%)	17(85.0%)			
Family history	Positive	6 (30.0%)[a]	12 (60.0%)[a]	0 (0.0%)[b]	17.143*	0.000	NS
	Negative	14 (70.0%)	8 (40.0%)	20 (100.0%)			

Table (2) shows that vitamin D deficiency was prevalent more among cystic fibrosis patients then non cystic fibrosis bronchiectasis patients then in controls (75%, 45% & 10% respectively) with high significance statistically, while vitamin D insufficiency was prevalent more in non CF patients then CF patients then controls (40%, 20% & 15% respectively), and vitamin D sufficient levels detected more in control group then bronchiectasis group then CF patients (75%, 15% & 5% respectively).

Table (2): Shows vitamin D level in the 3 studied groups

		Group A	Group B	Group C	Test value•	P-value	Sig.
		No. = 20	No. = 20	No. = 20			
Vit d 1st sample	Deficient	9 (45.0%)	15(75.0%)	2(10.0%)	23.978	0.000	HS
	In sufficient	8 (40.0%)	4 (20.0%)	6 (30.0%)			
	sufficient	3 (15.0%)	1(5.0%)	12(60.0%)			

Table (3) shows that % of improvement of vitamin D level after vitamin D supplementation for 6 months was more in group A (non CF patients) than in group B (CF patients) with high significance statistically (80%, 59% respectively)

Table (4) shows that there is highly significant change in severity of exacerbation in both groups after vitamin D supplementation, % of improvement in severity of exacerbation is more in non-cystic fibrosis bronchiectasis than in cystic fibrosis bronchiectasis.

Table (5) shows that degree of improvement in FEV1 in group A (non CF bronchiectasis) improved by 16 % & in group B by 15% which is highly significant statistically & that degree of improvement in FVC in group A (non CF bronchiectasis) improved by 11 % & in group B by 14% which is highly significant statistically & that degree of improvement in FEV1/FVC in group A (non CF bronchiectasis) improved by 8 % & in group B by 13% which is highly significant statistically.

Table (3): Shows vitamin D level in the 3 studied groups & % of improvement in Vitamin D level after Vitamin D supplementation:

		Group A	Group B	Group C	Test value•	P-value	Sig.
		No. = 20	No. = 20	No. = 20			
Vit d 1st sample	Mean± SD	21.65 ± 9.10	20.15 ± 11.66	35.68 ± 12.99	11.05	<0.001	HS
	Range	10 – 50	11 – 66	18 – 56			
Vit D 2nd sample	Mean ±SD	33.40 ± 7.92	36.30 ± 11.09	35.68 ± 12.99	0.397	0.674	NS
	Range	25 – 55	23 –69	18 – 56			
Paired t-test	P-value	<0.001	<0.001	---			
% of improvement	Median (IQR)	59.82 (33.3 – 82.57)	88.3 (72.8 – 113.94)	--	2.164≠	0.030	S
	Range	10 – 160	4.55 – 200	--			

•: One Way ANOVA test; ≠: Mann-Whitney test

Table (4): Shows relation between vitamin D level and degree of exacerbation in both groups:

		Group A		Group B		Test value*	P-value	Sig.
		No.	%	No.	%			
exacerbation	No	0	0.0%	0	0.0%	2.613	0.271	NS
	Mild	3	15.0%	4	20.0%			
	Moderate	11	55.0%	6	30.0%			
	Severe	6	30.0%	10	50.0%			
Exacerbation after vitamin D supplementation	No	2	10.0%	3	15.0%	1.682	0.641	NS
	Mild	13	65.0%	10	50.0%			
	Moderate	5	25.0%	6	30.0%			
	Severe	0	0.0%	1	5.0%			
% of improvement after vitamin D supplementation		**60%**		**35 %**				
P-value		**0.001 (HS)**		**0.005 (HS)**				

Table (5): Shows pulmonary function tests results in both CF & non CF bronchiectasis before and after vitamin D supplementation:

		Group A No. = 20	Group B No. = 8	Test value	P-value	Sig.
FEV`1						
Before	Mean ± SD	69.54 ± 9.53	75.38 ± 10.20	-1.436•	0.163	NS
	Range	40 – 82	65 – 96			
After	Mean ± SD	80.85 ± 8.79	85.25 ± 7.27	-1.252•	0.222	NS
	Range	63 – 102	78 – 100			
Paired t-test		**-7.603**	**-6.509**			
P-value		**0.000 (HS)**	**0.000 (HS)**			
% change	Median (IQR)	16.75 (6.83 – 23.13)	15.16 (7.56 – 18.96)	-0.636ǂ	0.525	NS
	Range	4 – 57.5	4.17 – 22.86			
FVC						
Before	Mean ± SD	78.79 ± 12.03	70.00 ± 9.38	1.847•	0.076	NS
	Range	57 – 100	58 – 90			
After	Mean ± SD	88.55 ± 12.16	80.50 ± 11.20	1.616•	0.118	NS
	Range	70 – 108	70 – 105			
Paired t-test		**-5.280**	**-11.341**			
P-value		**0000 (HS)**	**0.000 (HS)**			
% change	Median (IQR)	11.04 (5.04 – 21.02)	14.17 (13.34 – 17)	-0.534ǂ	0.593	NS
	Range	-8.24 – 35.09	10.29 – 20.69			
FEV1/FVC						
Before	Mean ± SD	78.63 ± 15.45	88.71 ± 10.70	-1.589•	0.125	NS
	Range	60 – 111	80 – 111			
After	Mean ± SD	86.61 ± 17.48	106.00 ± 6.45	-2.838•	0.009	HS
	Range	62.5 – 117	100 – 116			
Paired t-test		**-5.005**	**-4.508**			
P-value		**0.000 (HS)**	**0.004 (HS)**			
% change	Median (IQR)	8.76 (4.3 – 15.07)	13.64 (9.89 – 32.53)	-1.910ǂ	0.056	NS
	Range	-2.86 – 34.15	4.5 – 38.75			

4. Discussion

Cystic fibrosis (CF) is the most common lethal autosomal recessive respiratory disease in the western world with an estimated incidence of 1 per 300 live births. Most patients with CF succumb to respiratory failure from chronic pulmonary failure infections **(Eastham et al., 2014)**

Non-cystic fibrosis (non-CF) bronchiectasis often start in childhood with a significant impact on morbidity. Bronchiectasis is conventionally used as a descriptive term for an irreversible pathological state characterized by chronic suppurative airway disease manifested clinically by chronic productive cough and radiologically by bronchial dilation and often thick-walled bronchi. The mechanisms by which vitamin D may exert its beneficial actions in bronchiectasis are likely related to the role vitamin D in modulating the adaptive and innate immune response. Higher vitamin D status is associated with better pulmonary function and that vitamin D therapy may help recovery from pulmonary exacerbations of bronchiectasis in both CF & non-CF patients **(Cutting, 2015).**

The present study was conducted on 20 cystic fibrosis patients, 20 non cystic fibrosis bronchiectasis patients, 20 controls. Vitamin D serum level was measured in CF & non CF bronchiectasis patients and controls & pulmonary function tests were done to the patients prior starting vitamin D supplementation then vitamin D serum level was followed up in the patients after treatment & also pulmonary function tests were repeated. Controls were assessed by basal serum vitamin D level.

They were 40 patients, having a mean age of 7.35 ± 4.67 years (ranged from 1-17 years) and a mean duration of ds of 7.45 ± 3.97 years (ranged from 6 months to 15 years).

In this study, there was male predominance with male: female ratio (1.8: 1), we detected male predominance in cystic fibrosis patients (75%) while in non-CF bronchiectasis male predominance is 55% while Maria Moustaki and her colleagues reported

that there was no significant difference between males and females and found that incidence of bronchiectasis equal in both sexes. However in a systematic review concerning pediatric bronchiectasis, 55% of the participants were males.

Consanguineous marriage is more prevalent in CF more than non CF patients.75% of CF patients had consanguineous parents (15 cases), while 60% of non CF bronchiectasis cases had consanguineous parents (12 cases).

A large number of patients (18 patients) had positive family history of same condition (45% of cases). Family history is more prevalent in cystic fibrosis patients than non CF bronchiectasis patients. 6o% of CF patients (12 cases) had history of similar condition & sib death with same condition, while only 30% of non CF bronchiectasis patients had positive family history of same condition.

In current study with total bronchiectasis patients (both CF & non CF groups), 24 patients (60%) were vitamin D deficient, defined as vitamin D level below 2o ng/ml and 12 patients (30%) were vitamin D insufficient, defined as vitamin D level from 20 - 30 ng/ml and 4 patients (10%) were vitamin D sufficient, defined as vitamin D level above 30 ng/ml & the control group showed 2 individuals with deficient Vitamin D level (10%), and 6 individuals with insufficient vitamin D level (30%), and 12 individual with sufficient vitamin D level (60%).

75% of patients with CF in our study were vitamin D deficient (15 patients), 20% were vitamin D insufficient (4 patients) and only 5% were vitamin D sufficient (1 patient only) & then % of improvement in vitamin D level of CF patients after receiving vitamin D supplementation for 6 months was 88.3 % (72.8-113.94) (P-value <0.001) (highly significant statistically).

While only 45% 0f non CF bronchiectasis patients were vitamin D deficient (9 patients), 40% were vitamin D insufficient (8 patients) and 15% were vitamin D sufficient (3 patients) & then % of improvement in vitamin D level of non CF patients after receiving vitamin D supplementation for 6 months was 59.82 % (33.3-82.57) (P-value <0.001) (highly significant statistically).

In our study it was found that vitamin D deficiency was prevalent more among cystic fibrosis patients then non cystic fibrosis bronchiectasis patients then in controls (75%, 45% & 10% respectively), while vitamin D insufficiency was prevalent more in non CF patients then CF patients then controls (40%, 20% & 15% respectively), and vitamin D sufficient levels detected more in control group then bronchiectasis group then CF patients (75%, 15% & 5% respectively).

In 2013, Chalmers JD found in a case control study with non CF bronchiectasis patients that 50% of patients were vitamin D deficient and 43 % were vitamin D insufficient and only 7 % were vitamin D sufficient **(Chalmers et al., 2013).**

In 2017, a study done on 402 patients with non CF bronchiectasis in Scotland, patients were assessed for vitamin D level and classified as 50% vitamin D deficient, 43% vitamin D insufficient and only 7% were vitamin D sufficient.

Pulmonary function tests done to all our patient at the beginning of the study and then follow up done after medical treatment with vitamin D for 6 months then pulmonary function tests repeated, Spirometry was done for children older than six years.

We classified patients who performed spirometry according to severity of the FEV1. The interpretive strategy set out by the American Thoracic Society/ European Respiratory Society (ATS/ERS) task force suggests mild abnormalities being greater than 70%, moderate 60% to 69%, moderately severe 50% to 59**%,** severe 35% to 49%, and very severe less than 35% of predicted values **(Pellegrino et al., 2015).**

In our study as regard both CF & non-CF bronchiectasis patients, it was detected that in patients with deficient vitamin D level they have lower FEV1 than patients with sufficient vitamin D level & after vitamin D supplementation severity of the PFTs decreased in CF patients by 35% & in non-CF patients by 15 %.

Also we proved in our study that there is significant improvement in parameters of pulmonary functions, in both CF & non CF patients after receiving vitamin D for 6 months.

At 2014, Renata Ongaratto performed PFTs for 29 patients with cystic fibrosis, 62% showed mild to moderate abnormalities, 28% showed moderate to severe abnormalities & 10% showed severe abnormalities. also in that study it was found that subjects with low vitamin D level (less than 30ng/ml), had more than twice exacerbations than subjects with sufficient vitamin D levels in a 2 year period after vitamin D measurement**.**

A randomized double blind controlled trial included 30 cystic fibrosis patients admitted with pulmonary exacerbation, subjects who received Vitamin D had better antibiotic therapy free days and 1 year survival **(Grossmann et al., 2012).**

At 2012, Wolfenden LL detected in a retrospective cohort study that vitamin D status was positively associated with FEV1 in patients with CF & that the higher the vitamin D level the better lung functions and lower rates of pulmonary exacerbation **(Wolfenden et al., 2012).**

A study done at Edinburgh, Scotland 402 patients bronchiectasis participants were assessed for

vitamin D level, these patients were admitted with sever flare for 1 year period, it was proven that patients with deficient levels had more pulmonary exacerbations in comparison to insufficient and sufficient groups.

Conclusion

There is an association between vitamin D deficiency and bronchiectasis (both CF & non-CF). It was found that bronchiectasis patients are more vitamin D deficient than normal population. The more deficiency in Vitamin D, the more sever the lung disease. Vitamin D deficiency is also associated with more risk for pulmonary exacerbations (IV antibiotics need, hospital stay, ICU admission and missed school days)

Improving vitamin D status in bronchiectasis patients leads to improvement of pulmonary functions, less frequent & less sever exacerbations & hospital stay.

Vitamin D in doses sufficient to achieve serum levels > 30 ng/mL, has been part of the standard treatment for CF since many decades ago. Vitamin D desirable serum levels reflect our current knowledge on preserving bone health.

However, the issue of dose will become much more complex if we consider administering vitamin D for lung diseases, since we have to take into account the - yet unknown - levels required for its extra-skeletal functions. To make matters more complicated, a given dose of vitamin D will not necessarily attain the same increase of 25(OH)D serum levels in all patients.

The required daily doses to reach optimal levels for bone health, vary greatly in patients ranging from 400 to 5000 IU daily. The dose needed in order to attain the vitamin's maximum immune-modulatory function is probably higher than the dose required for optimal bone health.

This apparent paradox is due to the fact that vitamin D function in tissues is exerted mainly by the locally produced1,25(OH)2D. Indeed, lung epithelial cells express high levels of 1a-hydroxylase and are able of producing locally high levels of 1,25(OH)2D. When these cells were supplemented with 1 mmol/L of 25(OH)D, they produced 600 pmol/L of 1,25(OH)2D.

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