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THE IMPACT OF VITAMIN D SUPPLEMENTATION IN PAEDIATRIC PRIMARY CARE ON RECURRENT RESPIRATORY INFECTIONS: A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Paediatric respiratory tract infections (RTIs) are among the most common reasons for both physician visits and hospital admissions, being associated with significant morbidity and mortality. Evidence suggests that vitamin D supplementation may enhance the immune system of the host. We performed a randomised controlled trial to evaluate the impact of vitamin D supplementation on recurrent respiratory tract infections (RRTIs) in children attending paediatric primary care. We enrolled 77 children, in a primary care setting, who had been diagnosed with recurrent respiratory tract infections (RRTIs) (≥ 6 RTIs per year). 40 of these patients were randomly assigned to the group which received a vitamin D supplement (400 UI/day) from October to March, whereas the remaining 37 patients did not receive any supplementation. The number of RTIs, the duration of respiratory symptoms, the use of antibiotics and the number of physician visits during the study were recorded by parents using a structured diary. Both groups of children had similar baseline characteristics. During the study, significant differences ($p<0.05$) were found in vitamin D-supplemented group compared to the control group regarding the average number of RTIs (respectively 3.89 ± 2.49 vs. 6.35 ± 3.22), upper respiratory tract infections (URTIs) (2.97 ± 1.89 vs. 4.43 ± 2.85) and lower respiratory tract infections (LRTIs) (0.92 ± 1.14 vs. 1.92 ± 1.85), duration of respiratory symptoms in days (4.2 ± 2.61 vs. 6.86 ± 4.73), use of antibiotics (1.77 ± 1.35 vs. 3.7 ± 2.28) and number of physician visits (3.97 ± 2.32 vs. 6 ± 3.19). According to our data, vitamin D supplementation in children attending primary care settings may reduce the burden of RRTIs. Further and larger studies are needed to confirm our data.

1. Introduction

The Paediatric RTIs are one of the most common reasons for physician visits and hospital admissions, being associated with significant morbidity and mortality.

The Italian Society of Paediatrics defines RRTIs as either >6 RTIs per year or >1 RTIs per month involving the upper airways (URTI) from September to April - or >3 RTIs per year involving the lower airways (LRTI) [1].

Epidemiological data shows that 15% of children suffer from RRTIs with a consequent significant cost for both families and the wider society [2].

Several factors have been related to the occurrence of RRTIs: relative immaturity of the immune system, domestic and environmental pollution, atopy and virus infections. Despite RTIs being due mainly to viral infections, bacterial super-infections which are aggravated by increasing antibiotic resistance, occur more frequently nowadays [3].

Recurrence represents a challenge for paediatricians, so there is a growing interest in prophylactic treatments.

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Very recently, vitamin D, a well-known regulator of calcium and phosphate homeostasis, was found also to have extra-skeletal effects, including an influence on the immune system [4]. The impact of vitamin D is mediated by receptors (VDRs) that are located in various tissues [5]. As most immune cells express VDRs, vitamin D is thought to improve immune function and reduce inflammation through pleiotropic mechanisms [6].

Plasma concentration of vitamin D is strongly affected by the season, sun exposure, age, ethnicity, VDR polymorphisms, skin characteristics and fat absorption. A level between 20 and 50 ng/ml of vitamin D in plasma is thought to be adequate enough to provide an immunomodulatory effect [7].

Many studies suggest that vitamin D deficiency predisposes patients to RTIs, with an inverse correlation between vitamin D serum concentration and the occurrence of RTIs [8].

The evidence that viral infections are more common during winter, when vitamin D synthesis is impaired by reduced sun exposure, supports this association and suggests that adequate intake of vitamin D may be effective in reducing infections. [9]

It has been reported that adequate vitamin D intake may be an effective and inexpensive preventive measure against RTIs. Therefore, supplementation of vitamin D could reduce the number of incidences, severity and duration of RTIs.

In 2013, a meta-analysis showed that vitamin D supplementation protects against RTIs. Once daily administration of vitamin D, was seen to be most effective during this meta-analysis. However, the best supplementation regimen has not yet been clearly defined. [10]

Consequently, we designed a prospective, single-blind, clinical trial to evaluate whether oral supplementation of vitamin D from October to March could reduce RRTIs in a primary care setting.

2. Methods

Study design, patients and intervention

This was a single blind, randomized, controlled, clinical trial (Clinicaltrial.gov - NCT02617771), undertaken to assess the efficacy of vitamin D3 supplementation (400 IU/day) on incidence and severity of RTIs in children with RRTIs.

The study was carried out in a paediatric primary care outpatient clinic within the Italian National Health System of Southern Italy (ASL Bari) in collaboration with the Department of Biomedical Sciences and Human Oncology of the University of Bari.

Children were randomly allocated to one of two groups receiving either 400 IU of vitamin D3 per day in the form of oil drops, following the 2008 American Academy of Paediatrics recommendation [11], or no supplementation (Figure 1).

Parents were instructed that their infants should be given drops once daily by mouth, preferably in the morning, from 1st October 2014 to 31st March 2015. As a measure of compliance, the parents were asked to return the used bottles to the university personnel.

No specific dietary restrictions during supplementation were recommended, however, no other commercial products containing vitamin D were allowed.

Randomization was performed using a free web-based service that offers random assignment of participants to each group, taking into consideration gender, age (up to 12 months of age and beyond 1 year) and class. One of the authors (MEB) gave anonymous medication to parents who were then asked to return used bottles to evaluate compliance.

The primary care practitioner (RG) was blind to the group allocation of each child within the study group and was provided with no information from parents about vitamin D supplementation.

Inclusion criteria were:

a) Children from 0 to 84 months of life (< 7 years old).

b) ≥ 6 RTIs per year OR ≥ 1 RTIs per month from September to April involving the upper airways OR ≥ 3 RTIs per year involving the lower airways. The number of infections had been calculated from October 2013 to September 2014 (the 12 months prior to the starting date of the study).

c) No findings suggestive of an immunodeficiency on history and physical examination.

An exclusion criterion was dark-skinned ethnicity (V – VI Fitzpatrick skin type).

The primary outcome measure was the number of URTIs and LRTIs per person per year calculated from 1st October 2014 to 31st September 2015.

Secondary outcome measures were: days with RTI symptoms, number of visits to a physician due to RTI symptoms, number of infections needing antibiotic treatment and number of asthma attacks per person per year.

Other outcome measures were some direct and indirect costs related to RTI and Vitamin D supplementation.

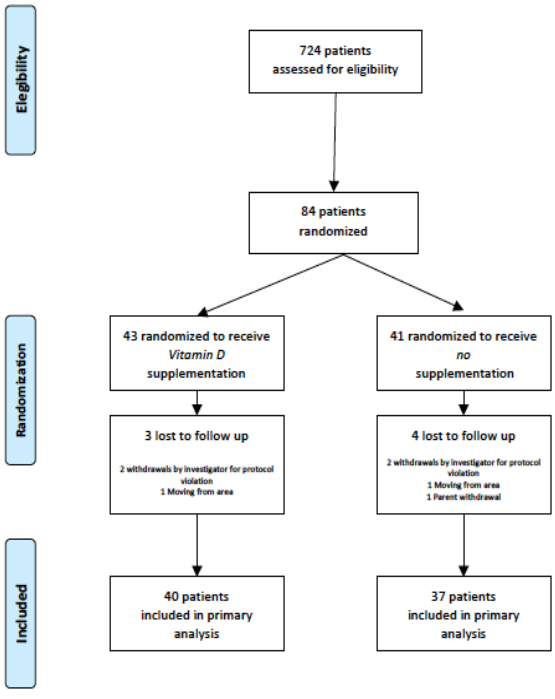

Figure 1 – Study flow

The sample size was established assuming a protective effect of vitamin D supplementation on the frequency in incidence of RTIs as shown in a previous study (11) (RR=0.52; confidence interval 95% 0.31-0.89; p=0.047), with α=0.05 and power=0.90, the minimum sample size was 33 per group. Considering a dropout rate of 20%, we enrolled 40 children per group.

Respiratory tract infection assessment

From the recruitment and for 12 months after, parents recorded any RTIs, the number of visits to a physician, the use of any antibiotics and the duration of symptoms using a structured diary. Adverse events related to the protocol were also recorded.

URTIs and LRTIs were defined, diagnosed and managed according to Italian National guidelines for outpatient setting: URTIs encompassed acute otitis media (AOM) [12] acute rhinosinusitis [13] and acute pharyngotonsillitis [14], while LRTIs included bronchiolitis [15] and pneumonia [16].

An episode of RTIs was considered to have finished when the child was symptom free for at least a day. A new episode was recorded after at least seven days without symptoms or fever.

All parents were in communication with one of the authors in the case of any concerns regarding the diary compilation.

The primary care practitioner collected the diaries at the end of the study and any missing data was retrieved through the database of the primary care practitioner himself. Data were recorded in a database created by Google Drive and data analysed by Stata MP13.

Quantitative data was expressed as mean and standard deviation (SD). Normality distribution of quantitative variables was examined and for upper RTI, antibiotic use, symptom duration and number of asthma attacks, normalization models were used. Student's t-test for unpaired data was used to compare upper and lower RTIs, paediatric visits and use of antibiotics between the two groups. Lower RTIs were not normal and the normalization model was not consistent, so the variable was described as median (IQR) and the Kruskal-Wallis test was used to compare the two groups. The χ^2 test was used to compare gender differences, whether or not the child was breastfed, the prevalence of asthma and allergy, family history of allergy and parental smoking between the two groups.

Multivariate regression models were designed to evaluate the role of confounding factors such as gender, age, BMI, breastfeeding, asthma, allergy, family history of allergies and parental smoking for selected outcomes.

For all tests, p-values <0.05 were considered significant.

Economic impact evaluation

Direct charges for the Italian National Health System were the following:

- Medical examination (€20.66 for each examination, provided by the Italian Ministry of Health).
- Antibiotics (cost according to the list of the National Drug Authority), at the dosage recommended by current guidelines.
- Vitamin D (cost according to the list of the National Drug Authority).

We also evaluated the number of work days lost by at least one of the parents for each day of symptoms. The cost of a day was set at € 46.29, as provided by Italian Law (D.M. 25 Giugno 2015, Gazz. Uff. 15 Luglio 2015, n. 162).

3. Results

84 children were initially involved in the study and 77 completed the entire follow-up period. Of these 77 patients, 40 were randomly assigned to a group receiving vitamin D oral supplementation and the control group constituted of 37 patients (Figure 1).

Dropouts at follow-up occurred due to: protocol violation (4 patients), voluntary withdrawal by parents (1 patient) and patients moving to another primary care practitioner (2 patients).

Demographic characteristics are described in Table 1 with no significant differences between the two groups, except for number of RTIs, in favour of the treatment group.

	Intervention group	Control group	p-value
Age in months, mean ± SD*	36.1 ± 14.1	34.7 ± 13	0.33
Male, %	57.5	54.0	0.76
Siblings, mean ± SD	0.6 ± 0.6	0.6 ± 0.6	0.49
BMI (kg/m2), mean ± SD	15.9 ± 1.1	15.7 ± 1.5	0.45
Breastfed, %	79.4	85.7	0.70
Breastfed duration in month, mean ± SD**	5.53 ± 6.1	3.7 ± 7.1	0.08
Asthma, %	50	48.6	0.90
Allergy, %	15	8.1	0.16
Family history of allergy, %	52.5	32.4	0.07
Parental smoking, %	37.5	40.5	0.78
Respiratory tract infections in the previous year, mean ± SD	2.9 ± 1.8	2.2 ± 1.4	0.04

*SD: standard deviation

** this variable has been normalized use square root function

Table 1 - Characteristics of children at baseline, according to their randomly assigned group

At the end of the 12-month follow-up period, the number of RTIs, both URTIs and LRTIs, was found to be statistically different between the two groups. Moreover, the number of visits to the practitioner and the use of antibiotics were lower for children with vitamin D supplementation (Table 2).

	Intervention group	Control group	p-value
RTI, mean ± SD*	3.8 ± 2.4	6.3 ± 3.2	0.0002
Upper RTI, mean ± SD	2.9 ± 1.8	4.4 ± 2.8	0.0061
Lower RTI, N, Median (IQR)**	1 (0-2)	0 (0-2)	0.01
Duration of symptoms, days, mean ± SD	4.2 ± 2.6	6.8 ± 4.7	0.0002
Pediatric visits due to the symptoms, mean ± SD	3.9 ± 2.3	6 ± 3.1	0.001
Use of antibiotics, mean ± SD	1.7 ± 1.3	3.7 ± 2.2	0.00001
Asthma attacks, mean ± SD	1.7 ± 0.9	2.6 ± 2.6	0.08

*SD: standard deviation

**this value was not normally distributed; Median, IQR and non parametric test were used

Table 2 - Number of RTI episodes in children and their socioeconomic burden according to their randomly assigned group, at 12 months.

Neither hospital admission nor side effects related to vitamin D supplementation were reported. Mean numbers of asthma attacks were similar between the supplemented and the control group (1.76 vs. 2.68; p-value 0.08).

The multivariate regression model showed that the mean number of RTIs is related to vitamin D supplementation (coef -2.06, p=0.006). This finding appeared significant only for LRTIs (coef=-0.93; p=0.011) but not for URTIs (coef=-1.12; p=0.071). Antibiotic prescriptions and number of paediatric visits are both negatively related to vitamin D supplementation (coef=-1.89; p<0.0001 and coef=-1.54; p=0.032, respectively).

The mean health cost per child in the supplemented group ranged from €93.4 to €94.1 whereas in the control group it was roughly €138 (from €137.3 to €138.8). The average state expenditure for each patient from October to April ranged from €287.5 to €287.8 in the supplemented group and from €454.9 to €456.4 in the control group.

4. Discussion

Our real-life experience in a primary care setting provides some interesting data from a clinical, pharmaco-economic and social point of view.

According to our results, oral vitamin D supplementation in otherwise healthy children diagnosed with RRTIs, reduces the number of RTIs and their global socioeconomic burden, so that, the maintenance of an adequate Vitamin D status may be considered an inexpensive and effective method of preventing RTIs.

Several studies have demonstrated that Vitamin D supplementation is a possible preventive measure against RTIS.

Numerous studies have identified an association between inadequate vitamin D concentrations and a higher risk among infants and children with rickets. [17]

Studies published over the past twenty years have reported a connection between vitamin D insufficiency and an increased susceptibility and severity of tuberculosis (TB). [18]

Gradually, other RTIs in children have proven to be linked to vitamin D deficiency and several studies have been performed. In 2013, Marchisio et al. evaluated the effects of vitamin D daily administration for four months vs. a placebo in a group of 1-5 year-old children with recurrent AOM history. The study revealed that the number of children experiencing ≥1 AOM episode during the study period was significantly lower in the treatment group. Statistically significant differences also appeared in the time of onset of uncomplicated AOMs and of all AOMs. Finally, the likelihood of AOMs was significantly reduced in patients who had levels of vitamin D ≥ 30 ng/ml at the end of the treatment period [19].

It is also known that maternal levels of vitamin D in pregnancy correlate positively with neonatal and cord blood levels of vitamin D. Interestingly, low cord blood Vitamin D levels have been associated with an increased risk of RTIs in the first 2 years of life. In addition, Camargo et al. demonstrated that a higher maternal intake of Vitamin D during pregnancy might reduce the risk of recurrent wheeze in early childhood. For that reason, Vitamin D supplementation for pregnant women and infants may be a useful and effective strategy to reduce the incidence of RTIs.

Some prospective studies observed a negative correlation between maternal levels of vitamin D during pregnancy and morbidity due to respiratory infections in early life [20–22], although no other work has confirmed this association [23].

Moreover, in terms of neonatal age, , infants hospitalized in a neonatal intensive care unit for acute respiratory infections had vitamin D levels significantly lower compared to a healthy control group. [24]

The correlation between lower Vitamin D levels and a predisposition to RTIs has also been demonstrated in prospective studies carried out even beyond the first year of life. Specifically, a well-designed Canadian study, performed on 843 children aged 3-15 years, showed that vitamin D levels <30 ng/ml were linked to a 50% increase in risk of having at least one respiratory infection during the respiratory virus season, confirmed by virological examination.[25]

In our experience, vitamin D supplementation reduced the numbers of both URTIs and LRTIs, decreased the duration of symptoms, and therefore reduced antibiotic use and medical visits. It may by suggested, therefore, that the maintenance of adequate Vitamin D levels could be an effective and inexpensive prophylactic method against RTIs. Furthermore, the statistically significant higher incidence of RTIs at baseline in the intervention group might mean an underestimation of the effects of vitamin D supplementation, strengthening our results further.

Our findings are in accordance with a recent systematic review of meta-analyses and RCTs on the impact of vitamin D supplementation in preventing common respiratory tract infections [26].

To the best of our knowledge, no one has yet measured the socio-economic impact of Vitamin D supplementation in preventing IRR. Our cost assessment suggests an estimated mean saving for the Italian National Health System that ranges from €43.9 to €44.7 per child during the study period. The assessment model does not take into account indirect costs. The number of RTIs and the reduction of days with symptoms may be particularly important for parents, often obliged to be absent from work to care for their offspring, and for primary care setting practitioners, often over-engaged in managing these children. Furthermore, combating the recurrences can significantly contribute to the reduction of antibiotic use and, consequently, the rates of antimicrobial resistance that significantly affects their efficacy.

However, in our cohort no significant difference in the number of asthma attacks was reported between the two groups, despite other authors finding that vitamin D supplementation reduced asthma attacks in children [26-27].

We are aware of some limitations of our study. First, as this trial was an independent and no-profit study, there was no funding for a placebo with identical sensory properties in order to maintain a double-blind status. Furthermore, this study has a limited number of patients, plasma evaluation of vitamin D level at enrolment and during the study was not performed, and nutritional intake of vitamin D was not measured.

Finally, we were not able to measure the sunshine exposure of participants directly, although some real time measurement and ultraviolet exposure index were considered in predicting the production of vitamin D at the skin level [28].

However, because of the effect of the sun's angle, synthesis of vitamin D in the skin is thought to be impossible during at least part of the year at any latitude greater than 34 degrees (as in Bari, Italy, latitude: 41° N). [29]

Further, double-blind, placebo-controlled, randomized clinical studies should be performed on a larger scale, in order to provide a conclusive indication of the benefits of vitamin D supplementation in RTIs prophylaxis and to identify the best supplementation scheme associated with a successful outcome.

It is also very important to be aware of the definition of deficiency and insufficiency of Vitamin D and when and how to treat this condition.

5. Conclusions

Maintenance of adequate vitamin D status may really be an effective and inexpensive prophylactic method against RTIs, though a supplementation regimen has not been clearly defined. Further clinical trials are needed to determine the vitamin D concentrations associated with an increased risk of RTIs and the optimal vitamin D supplementation regimen according to the type of RTI.

Given the global health burden of RRTIs in a primary care setting, our promising data, which supports vitamin D supplementation in selected patients, needs to be confirmed in larger, double-blind, placebo-controlled, randomized clinical studies with direct measurement of sunshine exposure, vitamin D plasma analysis and vitamin D nutritional intake evaluation.

List of abbreviations:

AOM: acute otitis media
LRTIs : lower respiratory tract infections
RTIs: respiratory tract infections
RRTIs: recurrent respiratory tract infections
TB: tuberculosis
URTIs: upper respiratory tract infections
VDR: Vitamin D receptor

Trial Registration: Clinicaltrial.gov - NCT02617771

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