VI.F.1.b.49

APPA

16th APCP • 9th ASMIPS/PIT-IKA • 6th APCPN

CERTIFICATE OF ATTENDANCE

Presented to

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as Oral Presenter

16th Asia Pacific Congress of Pediatrics (APCP) 2018 and
9th Annual Scientific Meeting of Indonesian Pediatric Society (ASMIPS)/PIT-IKA 2018

SDGs and Reducing Inequalities: How Far Have We Come?

25-29 August 2018

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SK PB IDI No. : 02326/PB/A.4/08/2018 Participant: 18 Credits Speaker: 14 Credits Moderator: 6 Credits Committee: 3 Credits

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SK CPD IDAI FOR MODERATOR/PARTICIPANT: 1220/A.2.2/CPD-I/Apl/2018

Participant in this program has been accredited by Indonesian Medical Association with a maximum credit point (SKP): 20 and acknowledged as the CPD category 1 (Learning Performance) of the Indonesian Pediatric Society.

Asia Pacific Journal of Pediatrics and Child Health

Abstract Ref Number = APCP406 Oral Presentation

VITAMIN D LEVEL & TUBERCULIN CONVERSION AMONG UNDERFIVE CHILDREN WITH TB CONTACT HISTORY AFTER VITAMIN D SUPPLEMENTATION

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Background : Vitamin D status is associated with developing of tuberculosis infection especially in under-five children. We will describe vitamin D level and tuberculin conversion with TB contact history after vitamin D supplementation in children with TB contact history. Material : During March 2014-December 2015, we were performed a double blind randomized study to 66 children underfive with TB contact history, but healthy condition regarding to tuberculin skin test results.We gave twice single high dose (25.000 IU) vitamin D3 and placebo randomized alocation, at baseline and day 42, then follow up until 12 weeks. Tuberculin conversion was determined using tuberculin skin test, with positive diameter ? 10 mm after 72 hours. We examined vitamin D serum level by ELISA methods. Results : Before intervention mean of vitamin D level at intervention group less than placebo (24.33 + 7.5 vs 26.94 +8.61). After intervention the mean of vitamin D level at intervention group more higher than placebo (28.47 + 7.18 vs 27.67 + 9.02), but not significantly differences. Among 8 (12.1%) children with TST conversion, we found that at baseline no subject with sufficient vitamin D status, and after vitamin D supplementation there were 3 subject with sufficient vitamin D status at intervention group. Conclusions : We demonstrated that there were increase of mean vitamin D level after vitamin D supplementation, but neverthelees TST conversion remains occur

Keywords: vitamin D level tuberculin conversion TB contact history

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Vitamin D Level and Tuberculin Conversion after Vitamin D Supplementation among Under-five Children with Tuberculosis Contact History

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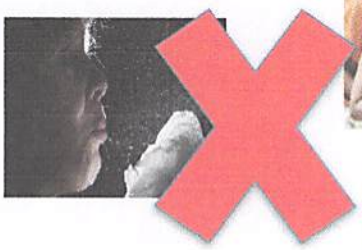
Tuberculosis transmitted

Children high risk ≤ 5 th



40-50% TB infection

1 million new TB disease in children
8-12% adult cases

<5th : Cause of death 2nd

WHO. Global Tuberculosis Report 2012

Introduction (1)

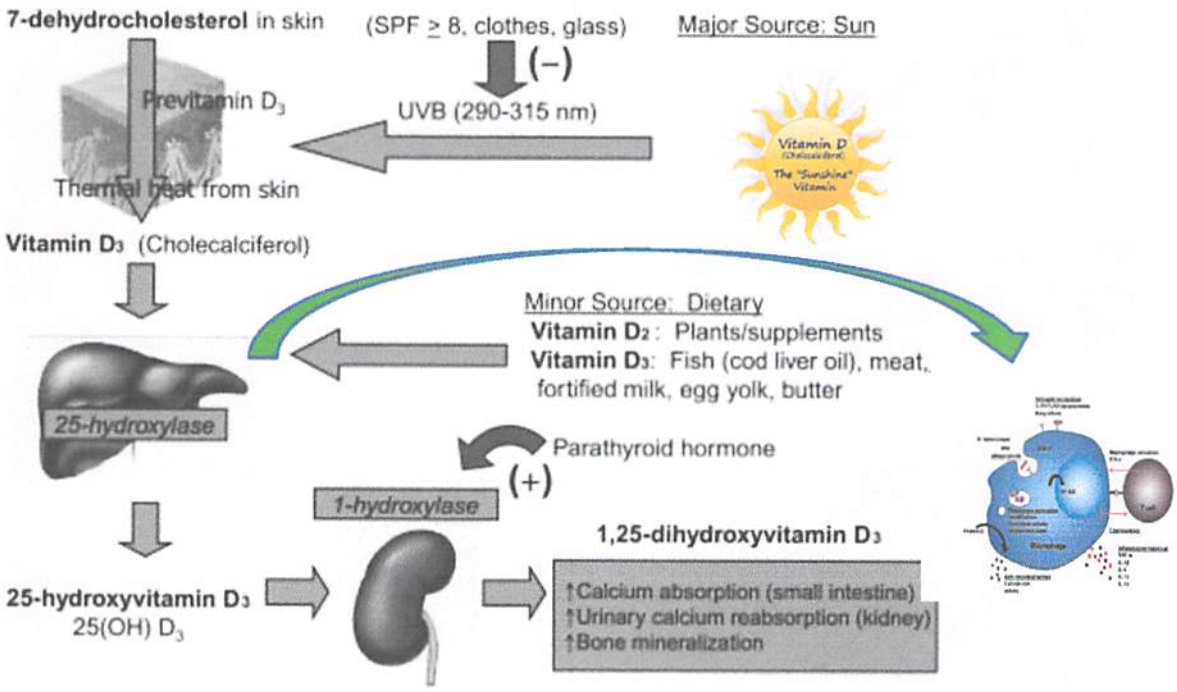
Introduction (2) :
Role of immunity to prevent TB infection

- Increasing immune system is the important things in children to prevent developing TB infection.
- Many clinical studies found association between vitamin D and TB
- There are many evidences that vitamin D supplementation have beneficial effect on immune system in general, particularly in childhood.

Immunomodulator ? → **Vitamin D ?**

Dheda K, etc.2010, Battersby AJ,. 2012, Hollick, 2008

Background (1) : Why vitamin D?



Hollick, 2008

Background (2)

- Study to adult TB contact gave a single dose of 2,5 mg vitamin D → ↑ immunity to mycobacteria → ↓ developing TB infection *Martineau, 2007*
- In Mongolian school-age children, vitamin D supplementation for 6 month, trend was seen toward fewer TST conversion in the vitamin D group. *Ganma, 2012*
- There were lacks of data about effect of vitamin D to prevent developing TB infection, especially in children under-five. Tuberculin skin test conversion is the way to know TB infection status

Objective

- This study aimed to find out the effect of vitamin D supplementation to healthy children under-five with TB contact history to prevent developing TB infection

Hypothesis

Proportion of TST conversion in vitamin D supplementation group less than placebo.

Methods (1)

- Population : children (≤5th) who had contact with smear positive adult TB patients (index cases) from 22 PHC in Padang city, West Sumatra
- From March 2014 to December 2016.
- Ethical approval : by ethical committee of Faculty Medicine Unand with 263/KEP/FK/2013.
- Study design is randomized double blind control trial methods.

Methods (2)

- **Inclusion criteria** : children ≤5th, close contact with positive smear adult TB for last 3 months, but had negative TST and no symptoms of TB at the initial assessment
- **Exclusion criteria** : had history of antituberculosis drug, severe malnutrition, and immune compromise conditions for last 3 months.
- Gender, age, and nutritional status was recorded & examined vitamin D blood level as baseline data.

Methods (3)

- **Intervention groups :** single high dose (25,000 IU) vitamin D_3 at **first day and 42th day (6 weeks)** ,
- **Placebo groups** : placebo drug
- Observed for **84 days (12 weeks)** and the end of observation we repeated tuberculin skin test and examined the vitamin D level.
- Vitamin D level was examined by **ELISA** methods at Prodia laboratorium & classified vitamin D level as **normal (>30 ng/ml), insufisiency (21-29ng/ml), deficiency (≤20 ng/ml).**

Methods (4)

- **TST** was considered **conversion** to positive if showing **induration ≥10** mm after 72 hours
- Statistical analysis using paired sample T test and chi square test. Data is considered significant if p value <0.05.
- Data analysis was done using *GraphPad Prism 7* software.

Results

- The total subjects in this study were 88 children,
- Intervention group : 42 children
- Placebo group : 46 children

Table 1 : Characteristics of research subjects

Characteristics	n	%
Gender		
Boys	33	37,5
Girls	55	62,5
Nutritional Status		
Obesity	1	1,1
Well-nourished	73	83,0
Mild Malnourished	12	13,6
Moderate Malnourished	2	2,3

More than half of children are girls (62.5%) and boys 37.5%. Most of them had wellnourished status (83.0%), but others mild-malnourished (13.6%), moderate-malnourished (2.3%) and obesity (1.1%).

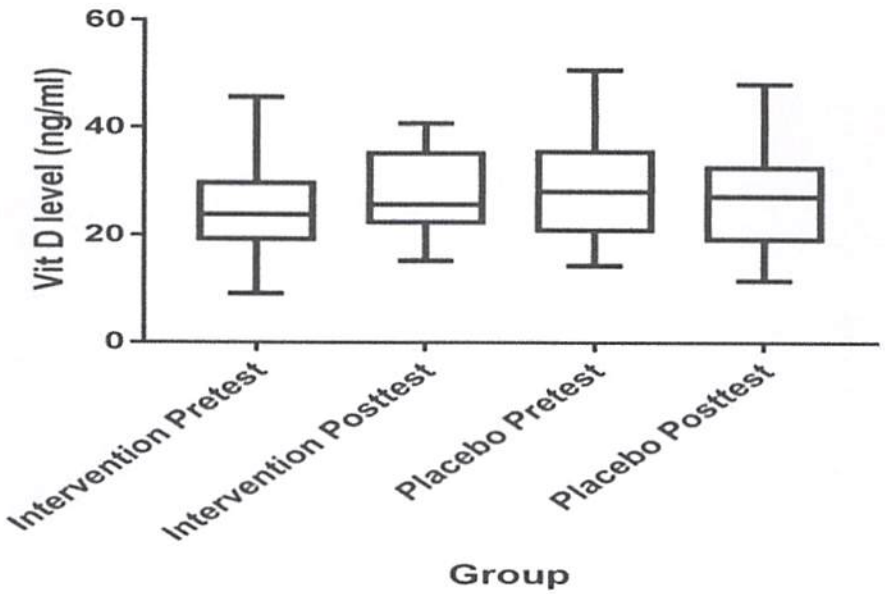
Table 2 : Mean differences vitamin D in levels at intervention and placebo groups

Group	Vitamin D (mean±SD)		p Value
	Pretest	Posttest	
Intervention	24.11±7.47	28.23±7.21	0.002*
Placebo	26.93±8.60	27.67±9.02	0.508

paired sample T test
*Significant p<0.05

- Mean of vitamin D levels in intervention group increase from 24.11±7.47 ng/ ml to 28.23 ± 7.21 ng/ ml after vitamin D suplementation.
- Result of statistic test showed that there was an effect of vitamin D in the intervention group ($p < 0.05$).
- There was no significant increase in vitamin D levels in the placebo group ($p > 0.05$).

Figure 1 : Differences in vitamin D levels between the intervention and placebo group



Vitamin D level higher in the intervention group than placebo after vitamin D supplementation.

Table 3 : The association between tuberculin conversion in posttest with intervention group and placebo

TST Results	Group		Total, n (%)	p Value
	Intervention, n(%) (n=42)	Placebo, n(%) (n=46)		
Positive	5 (55.6)	4 (44.4)	9 (100)	
Negative	37 (46.8)	42 (53.2)	79 (100)	0.731*
Total	42 (47.7)	46 (52.3)	88 (100)	

**Chi square*

Proportion of tuberculin conversion in the intervention group higher than placebo, but Chi-square test showed that there was no difference (p=0.731, p>0.05).

Table 4 : Association of vitamin D level with tuberculin conversion after intervention

Vitamin D	Tuberculin conversion		Total, n(%)	p value
	Positive, n(%)	**Negative, n(%)**		
Normal	4 (50.0)	21 (36.2)	25 (37.9)	
Insufficiency	1 (12.5)	28 (48.3)	29 (43.9)	0.118*
Deficiency	3 (37.5)	9 (15.5)	12 (18.2)	
Total	8 (100)	58 (100)	66 (100)	

**Chi square*

Children with normal vitamin D status, have the highest proportion of positive tuberculin (50.0%), followed by deficiency (37.5%) and insufficiency (12.5%), but no significant relationship (p=0.118, p>0.05).

Discussion (1)

- Supplementation of vitamin D in children under-five with TB contact history showing **vitamin D level were not significantly different** in both groups after the intervention.
- There was **an effect of increased vitamin D level** after vitamin D supplementation in the intervention group
- Vitamin D is an important micronutrient. Through out some mechanism as an imunomudulator to stimulate innate and adaptive immunity, vitamin D are able to kill *M.Tb*
- Many studies have suggested a positive association between vitamin D level and clinical improvement in TB patients.

Discussion (2)

- In this study at baseline data, mean of vitamin D 24.11 ng/ ml (intervention) and 26.93 ng/ ml (placebo) were insufficient status.
- This is not much different from other researchers.
- Low level of vitamin D in children, have an evidently high prevalence in the tropics and subtropics, although abundant of sunlight exposure for activating vitamin D precursor in the skin.
- (SEANUTS study) conducted a survey on the adequacy of nutritional intake of children in Southeast Asia, followed by 4 countries: **Malaysia, Indonesia, Thailand and Vietnam**

Discussion (3)

Country	Subject	Vitamin D status	Prevalence (%)	Mean Vitamin D level ng/mL
Vietnam	6-11.9 yo	deficiency	46.5 -58.9	21-29
Malaysia	4-6.9 yo	insufficiency	47.5	≤20 - 29
Thailand	3-5,9 yo	deficiency	24.5 -31.3	≤ 20 - 29
Indonesia	2-4.9	deficiency	14.4-77.5	
Yogyakarta*	Preschool age	insufficiency	36.1	
		deficiency	63.5	
This study baseline data	< 5 yo	insufficiency		24.11 & 26.93

The study found that overall there was a high prevalence insufficiency and vitamin D deficiency in children, but with varying degrees between countries. The low vitamin D level (<30 ng/ml) may increase the risk of under-five childrens with TB contact history to have TB infections

Discussion (4)

- This study showed after vitamin D supplementation, vitamin D level **increased** in the intervention group ($p=0.002$, $p<0.05$), but it was **not different** between the two groups ($p>0.05$)
- Vitamin D level **after intervention** has not reached to normal overall.
- This study revealed that vitamin D supplementation in the group intervention has not fully prevent for developing tuberculin conversion yet.
- Whereas the results showed in the intervention group the proportion of **positive** tuberculin conversion was **higher than** the **negative** 55.6% vs 46.8%.

Discussion (5)

- Tuberculin conversion was found in children with normal vitamin D status, but there was **no significant relationship** (p> 0.05)
- **Initial measurement of vitamin D level** : >1/2 of children had insufficient and deficient status, and with single high dose 25,000 IU vitamin D3 twice for 12 weeks has not reached the normal level
- It's not able to answer completely the role of vitamin D supplementation in tuberculin conversion, so **we need further study and analysis the fully effect.**

Limitation

- This study had limitations whereas some other factors could affect vitamin D level :
  - ❑geographic location
  - ❑duration of sunlight exposure daily
  - ❑type of food consumed and culture behaviour.

- We need to modify either dose or duration of vitamin D supplementation to obtain better results, and about the effects of supplementation by age group.
- There are the other factors that could influence the results including genetic factors of vitamin D receptor.

Conclusion

- The results concluded that there was an effect of vitamin D supplementation to increase serum vitamin D level.
- However, there was no association with the tuberculin conversion.
- It is recommended that healthy under-five children with TB contact history can be given vitamin D3 supplementation to increase vitamin D levels in serum so it can improve immunity response.

Funding

- This work was supported by the Indonesian **Danone Grant start from 2014 - 2016** and **Indonesian Pediatric SocietyGrant at 2013.**

Acknowledgment

- The authors would like to thank to Primary Health Care and team in Padang

Conflict of Interest

- The authors declare that they have no conflicts of interest
- This is a part of the doctoral dissertation of FFY at the Post Graduate Program Biomedical Medicine Faculty of Medicine Unand about vitamin D supplementation and role of some indicator to prevent TB infection
- The abstract was presented as an oral presentation at the 16th Asia Pacific Congress of Pediatrics (APCP), Bali, 25-29 August 2018

Thank You