

## Correlation Between Serum Uric Acid And Vitamin D in Male Patients of Pulmonary Tuberculosis Receiving 1<sup>st</sup> Line Antitubercular Therapy.

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### Abstract :

**Introduction:** vitamin d deficiency predisposes to development of active tuberculosis. High rate of deficiency of vitamin D have been found in patients receiving antitubercular treatment. Although there are not enough data to establish the efficacy of vitamin D supplementation on mycobacterium tuberculosis clearance from randomized control trial. Vitamin D enhances the expression of the anti microbial peptide cathelicidin(h CAP 18)in cultured macrophage in vitro. Antitubercular drug reduces the impact of vitamin D in enhancing cathelicidin production. Hyperuricemia is associated with low level of vitamin D, antitubercular therapy increases serum uric acid level. This study hypothesizes that hyperuricemia is associated with vitamin D deficiency which in turn make the individual more prone to develop active tubercular lesions.

### Objective:

1.To estimate serum uric acid and vitamin D level in patients of tuberculosis receiving 1<sup>st</sup> line antitubercular therapy and also in normal healthy male and to find out the correlation between them.

2.To find out the correlation of hyperuricemia and vitamin D deficiency with duration of antitubercular therapy.

**Methodology:** Study design:- A comparative study, 50 diagnosed pulmonary tuberculosis male patients and 50 healthy male volunteers were included. Blood sample were taken and serum uric acid and vitamin D level were estimated.

**Result:** Hyperuricemia and vitamin d deficiency was significantly more prevalent in patients receiving antitubercular therapy and hyperuricemia and vitamin D deficiency positively correlated with duration of the therapy.

**Conclusion:** Antitubercular therapy plays a significant role in increasing uric acid level and vitamin D deficiency and person with hyperuricemia and vitamin D deficiency are more prone to development of active tuberculosis infection.

**Keywords:** Antitubercular therapy, Cathelicidin,Hyperuricemia ,Toll like receptors, vitamin D insufficiency.

### I. Introduction

40% of Indian population (about 500 million) are estimated to be latently infected by Mycobacterium tuberculosis(MTB) and 2.2 million (4.4%) are supposed to develop active tubercular(Tb) infection each year(2015) which also include the newly infected person. Even after huge percentage of latently infected people very few of them develop active infection, this means that there are several factors which controls the infection and prevent its activation, probably multiple. Vitamin D is also one of them, but 80% of Indians are suffering from vit.D insufficiency or deficiency<sup>1</sup>. Several works have demonstrated preventive role of vit.D against Tb<sup>2,3</sup>. The active form of vit.D [1,25(OH)<sub>2</sub>D] has been shown to inhibit the growth of MTB through stimulating cell mediated immunity(CMI) and activating monocytes<sup>4</sup>. Studies on Gujarati living in the U.K. have found that lower level of vit.D is associated with increased risk of pulmonary Tb<sup>5</sup>. A recent systematic review and met analysis has suggested that individuals with Tb had lower level of vit.D than non Tb individuals<sup>6</sup>.

Active Tb is almost fatal if not treated but antitubercular treatment(ATT) is even not so smooth and easy going because of their side effects and adverse effects. Clinician treating Tb patients are even aware of their side effects, as Tb patients on first line conventional ATT takes more than one drug simultaneously and the regimen lasts from few months to almost two years or even more in some cases. As the duration of ATT passes on, more and more side effects appear up. Hyperuricemia is also one very well known side effect of ATT<sup>7</sup>. High prevalence of vit.D deficiency has been found in patients receiving ATT<sup>8</sup>. Previous work has shown higher prevalence of hyperuricemia in patients with vit.D insufficiency compared to those without vit.D

insufficiency<sup>9</sup>. Vit.D deficiency is a predictor of chronic kidney disease<sup>10</sup> and impaired renal function raises serum uric acid by decreasing its excretion<sup>11</sup>. Some works suggest that parathyroid hormone(PTH) has a significant biological influence on serum uric acid level<sup>12</sup>. Vit.D insufficiency induces release of PTH<sup>13</sup> and PTH is found to increase the incidence of hyperuricemia<sup>14</sup>. Previous works have also shown that antitubercular drug treated human macrophage like monocytic cells have significantly reduced production of the antimicrobial cathelicidin in response to vit.D in vitro<sup>15</sup>. These all prove that a vicious circle exist between hyperuricemia, vit.D insufficiency, reduced immunity to Tb, taking on ATT, ATT increases serum uric acid, ATT reduces protective effect of vit.D, vit.D insufficiency induces PTH release and PTH increases serum uric acid. The purpose of this study is to see whether a relationship exist between hyperuricemia and vit. D insufficiency both in patients taking ATT and normal healthy volunteers and also to see whether hyperuricemia and vit.D insufficiency are related with the duration of ATT course or not.

## II. Methodology

This comparative study was conducted on the diagnosed cases of pulmonary Tb attending DOTS center of Rajendra Institute of Medical Sciences(RIMS), Ranchi or diagnosed cases of pulmonary Tb who were admitted to Tb ward of RIMS. The period of this work was from January 2016 to April 2016. A total of 50 male patients taking ATT of age group 15years to 60 years were included. Tb was diagnosed by the presence of acid fast bacilli in smear from sputum or the isolation of MTB on culture. Control were age matched healthy male volunteers. Female were not included in this study because female reproductive hormones (estrogen) and menstruation are supposed to affect serum uric acid and vit.D level. Person having hypertension, diabetes mellitus, chronic alcoholics, hemolytic anaemia, any kind of bone disease or are taking vit.D supplement or any drug affecting uric acid level were excluded from this study.

8.0 ml of venous blood were drawn under aseptic condition in fasting state. Serum uric acid was estimated by automated chemical analyzer AU480 using Uricase methods( value below 7.1mg/dl were considered normal). Serum vit.D level was estimated by CMIA(Chemiluminescent Microparticle Immuno Assay) using antibody based Chemiluminescent immunoassay( value between 20-30ng/ml were considered vit.D insufficient, between 10-20ng/ml were considered moderately deficient and below 10ng/ml were considered severely deficient). Tests were performed in the Biochemistry department of RIMS. Data was analyzed by SPSS version 20. Mean and standard deviation(SD) were calculated to describe serum uric acid and vit.D level, these parameter of the two group were compared by independent sample t test. Pearson's correlation coefficient were calculated to check the linear correlation of serum uric acid and vit.D with each other and with the duration of antitubercular treatment.

## III. Result

1. The mean  $\pm$  SD value for serum uric acid and vit.D level in patients receiving ATT was  $7.6 \pm 1.4$  mg/dl and  $19.4 \pm 10.0$  ng/ml respectively in comparison to  $4.23 \pm 1.7$  mg/dl and  $29.4 \pm 9.8$  in healthy male volunteers respectively.
2. A significant positive correlation was found between serum uric acid and the duration of ATT with  $R=0.834$ ,  $P=0.000$
3. A significantly negative correlation was found between serum vit.D level and the duration of ATT with  $R= -0.798$ ,  $P=0.000$
4. A significantly negative correlation found between serum uric acid level and vit.D level or we can say that hyperuricemia is positively correlated with vit.D insufficiency.

<b>Table 1. comparison between mean serum uric acid and vit.D level in cases(1) and control(2) group</b>					
	group	N	Mean	Std. Deviation	P value
Uric acid(mg/dl)	1	50	7.650	1.4222	0.000
	2	50	4.213	1.7057	
vit.D(ng/ml)	1	50	19.460	10.0394	0.000
	2	50	29.417	9.8009	

**Table 2.** Linear correlation of serum uric acid and vit.D with each other and with the duration of ATT

	URIC ACID	VITAMIN D	DURATION OF ATT
URIC ACID		$R= -0.966$ $P=0.000$	$R=0.834$ , $P=0.000$
VIT D	$R=-0.966$ , $P=0.000$		$R=-0.798$ , $P=0.000$

#### IV. Discussion

Vit.D receptors(VDR) are also expressed by immune cells like T cells, B cells, dendritic cells and macrophages and expression of specific microbicidal peptides in macrophage is significantly influenced by vit.D and VDR<sup>16</sup>. This protective mechanism is applicable to common infections like Influenza and Tb. Active form of vit.D can inhibit the growth of MTB in cultured human macrophages<sup>17</sup>. MTB activates macrophage via the toll like receptors(TLR) complex to stimulate the expression of VDR and 1 alpha hydroxylase which convert 25(OH) vit.D into its active form<sup>18</sup>. Binding of active vit.D with VDR induces transcription and translation of various genes including the anti microbial peptide Cathelicidin(hCAP18) and its cleaved peptide LL-37 and also beta defensin 4(DEFB-4). Both hCAP18 and DEFB-4 stimulate the eradication of MTB via the auto lysosomal process<sup>19</sup>. Isoniazide can either induce or inhibit the cytochrome p450 system which may result in the alteration of 25 hydroxylase and 1alpha hydroxylase enzymes required for vit.D activation<sup>20</sup>. Ripampicin can increase CYP 3A4 dependent 25(OH) D<sub>3</sub> metabolism in liver<sup>21</sup>. Vit.D may alter the growing environment of MTB via PPAR by enhancing the antimicrobial effect that was induced by VDR<sup>22</sup>. Isoniazide may decrease the function of CD4 T cells via inducing apoptosis<sup>23</sup>. Decreased vit.D level causes increased secretion of PTH which in turn increases bone resorption and thus increased production of uric acid due to increased osteocytes turn over as chronic increase of PTH causes bone resorption<sup>24</sup>.

#### V. Conclusion

A vicious circle is created by hyperuricemia and vitamin D insufficiency which then makes the person more prone to develop active tubercular infection and drug used to manage this dragon like disease are themselves big dragon which further increases the morbidity related to these two co morbid conditions. Therefore a general awareness should be spread to supplement vitamin D in daily diet to strengthen our immunity against these life destroying diseases. As hyperuricemia is associated with vitamin D insufficiency, yearly screening should be done in individual at high risk or with family history of gout. If a patient attend an OPD with complain of pain and found to be hyperuricemic then his vitamin D level as well as renal profile should be checked for further management. General awareness should also be spread through social media for at least daily 10 minutes sun exposure, regular exercise(to prevent development of insulin resistance), avoiding high calorie diet and regular intake of vitamin and mineral and also essential amino acid to keep all glands working properly.

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