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Vitamin D status in peripheral vascular diseases: A longitudinal prospective study

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ABSTRACT

Background: Peripheral artery disease (PAD) is due to abnormal Narrowing of arteries other than heart and brain (primarily due to atherosclerosis). PAD is the most common form of PVD. **Aims and Objectives:** In the present study, we analyzed Vitamin D association with peripheral vascular diseases as well as coagulation and inflammation parameters. **Materials and Methods:** The study was conducted for 100 PAD patients of 18–70 years age and divided in Group I≤20ng/ml and Group II>20ng/ml for serum Vitamin D level. A single, oral, and high- dose Vitamin D3 supplementation 1,20,000IU was given in GroupI. At baseline and at the end of the study after 1 month, Ankle Brachial Index, modified Rankin Scale, Vitamin D, Inflammation and coagulation parameter, HbA1c, etc., were performed in all patients. Evaluation was done using SPSS. The level P<0.05 was considered as the cut off value of significance. **Results:** The majority of the PAD patients were Vitamin D deficient and have higher HbA1c level with statistically significant (P<0.05) association. This is because low Vitamin D is the risk factor for diabetes in which HbA1c level is higher. **Conclusion:** Asingle, oral, and high-dose Vitamin D3 supplementation did not alter parameters of inflammation and hemostasis in patients with peripheral arterial disease, adding more data to other studies that did not confirm a causal role of Vitamin D in cardiovascular disease.

Key words: Cardiovascular risk factors; Peripheral artery disease; Parathyroid hormone; Vitamin D deficiency

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INTRODUCTION

In peripheral artery disease (PAD) arteries other than heart and brain becomes narrow. PAD is the most common type of PVD. Hence, PVD is also known as arteriosclerosis obliterans (Peripheralarterialocclusivedisease[PAOD]). Atherosclerosis is a main reason of occlusion. Individuals over 40 years old are mostly the sufferer.[1]

There are changes in blood vessel structure due to inflammation, plaques, and tissue damage in response of cigarette smoking, diabetes, high blood pressure, kidney problems, and high blood cholesterol.[2] Such type of PVD is organic type. Functional PVD means there's no physical damage to the blood vessels' structure. Instead, the vessels widen and narrow in response to other factors like brain signals and temperature changes.

In primary care, diagnosis of PAOD is performed by measuring the ankle-brachial pressure index with a score<0.9, which is the systolic blood pressure at the ankle divided by the systolic blood pressure of the arm.[3]

According to the recent meta-analysis, PAOD is world wide prevalent, being greater in the elderly due to reduced expression of the Vitamin D receptor and thus reduced Vitamin D synthesis. Myopathy more marked in the proximal muscles develops a main contributor in the pathogenesis of PAD.[4-8]

serum 25(OH) Vitamin D<20ng/ml is diagnostic of Vitamin D deficiency. When serum 25(OH)D levels below 11–14ng/mL, there is increased chance of CVD risk.[9] Serum 25(OH)D>30ng/mL is optimal for bone health. Parathyroid hormone(PTH) suppresses, when Vitamin D

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levels reached between 30 and 40ng/ml.[10] Thus, Vitamin D deficiency induces hyperparathyroidism which may act on PTH receptors within the blood vessel wall and the myocardium leading to hypertension, cardiac dysfunction, and vascular disease.

Active Vitamin D calcitriol does many functions such as inhibition of endothelial cell activation and inflammatory cytokines IL-10 while reducing TNF-α adhesion molecule expression thus influencing the atherosclerotic process. It has protective effect on the heart through the renin-angiotensin hormone system, through the suppression of inflammation, or directly on the cells of heart and blood vessels walls. Serum 1α,25(OH)2D3 level is inversely related to the total (intimal and medial) coronary artery calcification and parameters of endothelial dysfunction and arterial stiffness.[11]

AIMS AND OBJECTIVES

In the present study, we analyzed the association of Vitamin D levels with peripheral vascular diseases and the effect of Vitamin D supplementationin Vitamin D deficient subjects on the status of PAD as well as coagulation and inflammation parameters.

MATERIALS AND METHODS

This was a hospital-based prospective study conducted over 100 PAD patients in GSVM Medical College (K.P.S Institute of Medicine and L.P.S Institute of Cardiology and L.L.RHospital), Kanpur (UttarPradesh) with age between 18 years and 70 years, of both sex from January 2019 to October 2020.

A total of 109 patients were screened, six were rejected to participate in the study and three were not fit according to the inclusion criteria and finally 100 patients were found fit according to the inclusion criteria.

All the patients were evaluated after obtaining the consent on the basis of semi-structured proforma in Local and Hindi language for sociodemographic details; history about diagnosis, treatment (present/past), adverse effects, and physical examination. Thereafter, routine clinical and radiological examinations were done to analyze severity of PAD.

Inclusion criteria

All patients in OPD and indoor were enrolled in this study. Patients with chronic PAD (defined as an ankle brachial index [ABI] <0.9, or angiographically based verification of a>50% stenosis or occlusion in a leg artery), unchanged medication in the 6 weeks prior to the study, no vascular interventions in the 2 months preceding the study, and patients who had given informed written consent were considered for inclusion criteria.

Exclusion criteria

While patients with Acute intercurrent illness, renal insufficiency (defined as serum creatinine>130μmol/l), acute myocardial infarction or stroke (within 2 months), on current oral anticoagulation medication, liver cirrhosis, and presence of any malignancy were considered for exclusion criteria.

Method of collection of data

About 5ml of venous bloodfasting (12–16h) was collected, fasting blood glucose was determined immediately, then the rest of the serum stored at −20°C for lipid profile and other hemodynamic measurements. Patients were divided in two group as GroupI (Serum Vitamin D≤20ng/ml) and GroupII (Serum Vitamin D>20ng/ml) on the basis of the previous study,[12] taking 20ng/dl as the reference range. A single and oral high-dose Vitamin D supplementation (120000IUVitamin D3) was done in Group I.

At baseline and at the end of the study after 1 month, ABI, modified Rankin Scale (mRS), blood collection, and specific tests were performed in all patients.

Patients with an ABI<0.9 were considered to have PAD and they were screened for serum Vitamin D level.

mRS is a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered with a stroke, PAD, or other causes of neurological disability.

Ethical committee

Institutional Ethical Committee approval was taken for this study.

Statistical analysis

Data were analyzed using Statistical Package for the Social Sciences, version 23 (SPSSInc.,Chicago,IL). The level P<0.05 was considered as the cut off value of significance.

RESULTS

In this longitudinal prospective study, it was found that the majority of the patients were having Vitamin D deficiency (70.0%).

(Table 1) p value was found to be<0.05 at 95% C.I. Hence, the association was statistically significant.

Table 1: Distribution of patients on the basis of their Vitamin D status

Vitamin DIevel	Numberofpatients	%	Mean±S.D.
≤20ng/dl	70	70%	13.80±3.83
>20ng/dl	30	30%	24.39±2.27
Total	100	100%	

Chi-square; Unpaired Student's t test, P<0.05, C.I. 95%

The majority of the patients were males, 46–60 years, from the urban areas, from lower and lower middle class, had completed their Secondary Education, were employed and Hindu by religion, but our study shows insignificant statistically. LDL cholesterol was higher in both the groups as compared to HDL cholesterol and the association between the groups was found to be statistically insignificant (P>0.05) (Table 2).

Table 3 shows that HbA1c was significantly higher in Vitamin D deficient (≤20ng/ml) group and the association was statistically significant (P<0.05).

Table 4 shows that the ABI, % stenosis of peripheral artery, and mRS disability score for PAD and the association were statistically insignificant among the groups (P>0.05).

The coagulation and inflammation parameters before and after supplementation of Vitamin D were not changed significantly among the groups (P>0.05) (Table 5), their serum levels of calcium and phosphate and PTH in both groups were associated statistically insignificant (P>0.05).

DISCUSSION

Deficiency of Vitamin D has been associated with increased prevalence of multiple diseases including osteoporosis, a number of autoimmune diseases, many different cancers, and conditions such as hypertension and cardiovascular diseases (CVDs).[13]

The previous clinical and observational studies have indicated that low Vitamin D as according to the Endocrine Society guidelines (Rosen et al., 2012)[14] can impair vascular function by compromising vascular compliance manifesting as increased arterial stiffness.

No causal relationship has been established. Therefore, naturally, this has stimulated research into improving Vitamin D status to determine the impact of Vitamin D supplementation on these end-points.

In this longitudinal prospective study, the majority of the patients with PAD were having Vitamin D deficiency (70.0%). A single, oral, and high-dose Vitamin D

Table 2: Distribution of patients with PAD on the basis of their lipid profile in Vitamin D sufficient and deficient group

LipidProfile	Vitamin D (≤20ng/ml) (n=70)	Vitamin D (>20ng/ml) (n=30)	P-value
TotalCholesterol (mg/dl)	179.45±13.28	178.0±12.57	0.589
Triglycerides (mg/dl)	112.88±22.53	116.07±21.93	0.639
HDL-C (mg/dl)	46.1±9.36	48.5±10.06	0.224
LDL-C (mg/dl)	117.75±14.31	122.9±18.54	0.136

Student's t-test; statistically insignificant (P>0.05)

Table 3: Distribution of patients with PAD on the basis of their HbA1c in Vitamin D sufficient and deficient group

	Vitamin D (≤20ng/ml) (n=70)	Vitamin D (>20ng/ml) (n=30)	p-value
HbA1c(%)	7.43±1.61	6.86±1.92	<0.05

Student's t-test; statistically significant (P<0.05)

Table 4: ABI before and after supplementation

	Vitamin D deficient (≤20ng/ml) (n=70)	After supplementation (n=70)	P-value
ABI	0.53±0.18	0.59±0.21	0.463
Stenosis (in%)	71.78±11.68	70.96±12.64	0.691
mRS	2.32±1.02	2.38±1.21	0.752

Paired t-test; statistically insignificant (P>0.05)

Table 5: Coagulation and inflammation parameters before and after supplementation

	Vitamin D (≤20ng/ml) (n=70)	After supplementation (n=70)	P-value
PT (Sec)	10.57±1.60	10.82±1.54	0.348
aPTT (sec)	30.24±3.47	31.36±3.52	0.060
INR	0.84±0.23	0.92±0.29	0.073
CRP (mg/L)	2.66±1.7	2.97±1.4	0.545
ESR (mmperhr)	30.28±4.49	30.34±3.92	0.933
D-Dimer (mcg/ml)	0.9±0.26	0.97±0.28	0.768

Paired t-test; insignificant (P>0.05)

supplementation (1,20,000IU vitamin D3) did not alter parameters of inflammation and hemostasis in patients with PAD, adding more data to other studies that did not confirm a causal role of Vitamin D in CVD.

In the present study, it was seen that as the age increases the problem of PAD also increases while the association

was found to be statistically insignificant (P>0.05). The majority of the patients were in the age group ranging from 46 to 60 years and the mean age for the patients with Vitamin D ≤20ng/ml was 49.61±13.45 and that of Vitamin D>20ng/ml, it was 50.9±11.19 (P>0.05).

Our findings were consistent with Stricker et al.,2012[15] who reported the insignificant association between the ages among the two groups but the mean age was higher in their study which may be because their sample size was smaller than our study.[16] In their study based on Vitamin D deficiency may be an independent risk factor for arterial disease reported the mean age of the studied patients with severely deficient Vitamin D as 64.3 and 11.6 years while the overall mean age was 66.810.7 years which was slightly more than the present study but the association was statistically insignificant which was similar to the present study. Bonatto et al.,2020[17] reported that both the methods for PAD diagnosis as well as the participants' mean age were similar to those in their study (P>0.05).

In our study, it was seen that the majority of the studied patients were males than females in both the groups and the association was found to be statistically insignificant (P>0.05). Furthermore, all the other demographic parameters show no statistically significant difference among the two group (P>0.05). VandeLuijtgaarden et al.,2012[16] supported our findings in their study on Vitamin D deficiency may be an independent risk factor for arterial disease and reported that males were more prone to vascular disease and were in higher number in their study than females (P>0.05). Stricker et al.,2012[15] reported 61.0% males in their study, which was in accordance to the present study and the association was statistically insignificant (P>0.05). Yuan et al.,2019[18] and Satilmis et al.,2015[19] also reported similar finding as in the present study.

In the present study, the lipid profile parameters and serum calcium and phosphate were measured in all the patients of both the groups and there was no significant difference observed among the groups (P>0.05). Yuan et al.,2019[18] and Stricker et al.,2012[15] also supported our study.

In our study, the HbA1c level was higher in Vitamin D deficient group than in the group with Vitamin D>20ng/ml and the association was found to be statistically significant (P<0.05), this is because low Vitamin D is the risk factor for diabetes and in diabetes patients, HbA1c level is higher. Our findings were supported by Yuan et al., (2019)[18] who reported the level of HbA1c as 8.77±1.82 in one group and 9.12±1.71 in the other group but they were associated insignificantly (P>0.05). Satilmis et al.,2015[19] and Stricker et al.,2012[15] also reported similar findings as in the present study.

In our study, it was found that PTH was insignificantly associated between the groups (P>0.05).

Intact PTH and Vitamin D have been implicated as risk factors for CVD, being associated with increased rates of myocardial infarction, stroke, and heart failure, as well as an increased all-cause mortality (OR1.71for men and 1.85 for women) Slinin et al., 2005.[20]

Part of this increased risk stems from the recognition that hyperparathyroidism and Vitamin D deficiency result in multiple dysregulatory abnormalities including malignant myocardial and valvular calcification, disturbances in the renin–angiotensin system, and vascular endothelial cell dysfunction leading to increased arterial stiffness and resultant hypertension, left ventricular hypertrophy, and diastolic dysfunction Kiernan et al., 2006.[21]

ABI was the measurement used to diagnose PAD in our institute and these are the novel findings of our study which shows that Vitamin-D supplementation does not affect the peripheral vascular disease parameters (P>0.05).

All the parameters related to coagulation and inflammation show no significant difference before or after the Vitamin-D supplementation (P>0.05). D-dimer was 0.9±1.11mcg/ml and 0.97±1.25 mcg/ml, hs CRP was 2.66±2.7mg/L and 2.97±2.4mg/L, respectively, for ≤20ng/ml Vitamin-D group and for sufficient group, respectively. Similarly, other parameters were also related insignificantly among the groups.

Stricker et al.,[15] reported almost similar findings as in the present study for hs CRP (P=0.35) and D-dimer (P=0.53). There were no such previous studies which have focused on the parameters we have used in our study and these are the novel findings in the Northern part of India to see the association of Vitamin D status in peripheral vascular disease.

Other studies, however, support our results. In a randomized and controlled interventional trial, a 4-monthly oral 100000IU Vitamin D 3 substitution during 5 years in subjects more than 65 years old had no effect on total or cardiovascular mortality but prevented fractures Trivedi et al., 2003.[22]

In the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes trial, 5292 patients aged at least 70 years with osteoporotic fractures were randomized to 800 IU Vitamin D3 daily, 100 mg of calcium, both, or placebo. No effect on mortality or vascular disease was detected after a 3 years' follow-up Avenell et al., 2011.[23]

In a recent systematic review and meta-analysis of 51 randomized interventional trials did not find a significant effect of Vitamin D supplementation on death, stroke, myocardial infarction, lipids, and blood pressure Elamin et al., 2011.[24]

Thus,Vitamin D may have a fundamental role in reducing the risk of PAD and studies of Vitamin D supplementation for patients with PAD are urgently needed. In the meantime, adequate outdoor activity and sun exposure, along with Vitamin D supplementation (to reach serum 25-hydroxy Vitamin D levels of atleast 20ng/mL), should be considered for both the prevention and the treatment of PAD.

A sufficiently powered study is needed to definitely exclude an influence of Vitamin D on cardiovascular surrogate parameters such as arterial stiffness. The final answer whether supplementation of Vitamin D has an impact on CVD must attend the results of the eagerly a waited ongoing large-scale interventional trials.

Limitations of the study

- The sample size in our study was relatively small.
- As a single-center hospitalized study, the enrolled patients may be different from the actual demographic profile of Kanpur or Uttar Pradesh.

Strengths of the study

1. The data were analyzed on the basis of consent proforma.
2. In this well-defined subset of cardiovascular patients with PAD, we did an interventional study with a single and oral dose of Vitamin D, which circumvents problems with patient adherence regularly found in long – term studies.

Recommendations

A large, robust, well-designed RCTs, and prospective longitudinal studies are required to determine the potential causal nature of Vitamin D on arterial compliance and CVD risk independent of known risk factor.

CONCLUSION

Our findings support the association between deficient Vitamin D serum levels and PAD, and, as far as we know, this is the first North Indian study to research such association. In this experimental study, most patients with PAD (n=70) were Vitamin D deficient. Vitamin D supplementation increased serum 25-hydroxy Vitamin D without modifying disease severity, coagulation, and inflammation parameters, although the study was underpowered for definite conclusions.

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REFERENCES

1. Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: Executive summary: A report of the American college of cardiology/American heart association task force on clinical practice guidelines. J Am CollCardiol. 2017;69(11):1465-1508.
   https://doi.org/10.1161/CIR.0000000000000470
2. Fowkes FG, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: A systematic review and analysis. Lancet. 2013;382(9901):1329-1340.
   https://doi.org/10.1016/S0140-6736(13)61249-0
3. Ruiz-Canela M and Martínez-González MA. Lifestyle and dietary risk factors for peripheral artery disease. Circ J. 2014;78(3):553-559.
   https://doi.org/10.1253/circj.cj-14-0062
4. Song P, Rudan D, Zhu Y, Fowkes FJ, Rahimi K, Fowkes FG, et al. Global, regional, and national prevalence and risk factors for peripheral artery disease in 2015: An updated systematic review and analysis. Lancet Glob Health. 2019;7(8):e1020-e1030.
   https://doi.org/10.1016/S2214-109X(19)30255-4
5. Savji N, Rockman CB, Skolnick AH, Guo Y, Adelman MA, Riles T, et al. Association between advanced age and vascular disease in different arterial territories a population.J Am Coll Cardiol. 2013;61(16):1736-1743.
   https://doi.org/10.1016/j.jacc.2013.01.054
6. Gallagher JC. Vitamin D and aging. EndocrinolMetabClin North Am. 2013;42(2):319-332.
   https://doi.org/10.1016/j.ecl.2013.02.004
7. Bischoff-Ferrari HA, Borchers M, Gudat F, Dürmüller U, Stähelin HB and Dick W. Vitamin D receptor expression in human muscle tissue decreases with age.J Bone Miner Res. 2004;19(2):265-269.
   https://doi.org/10.1359/jbmr.2004.19.2.265
8. Rasheed K, Sethi P and Bixby E. Severe Vitamin D deficiency induced myopathy associated with rhabydomyolysis. N Am J Med Sci. 2013;5(5):334-336.
   https://doi.org/10.4103/1947-2714.112491
9. Tepper S, Shahar DR, Geva D, Avizohar O, Nodelman M, Segal E, et al. Identifying the threshold for Vitamin D insufficiency in relation to cardiometabolic markers. NutrMetabCardiovasc Dis. 2014;24(5):489-494.
   https://doi.org/10.1016/j.numecd.2013.10.025
10. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of Vitamin D deficiency: An endocrine society clinical practice guideline. J ClinEndocrinolMetab. 2011;96(7):1911-1930.
    https://doi.org/10.1210/jc.2011-0385
11. Wu-Wong JR. Potential for Vitamin D receptor agonists in the treatment of cardiovascular disease. Br J Pharmacol.

2009;158(2):395-412.

https://doi.org/10.1111/j.1476-5381.2009.00171.x

12. McDermott MM, Liu K, Ferrucci L, Tian L, Guralnik J, Kopp P, et al. Vitamin D status and functional performance in peripheral artery disease. Vasc Med. 2012;17(5):294-302.

    https://doi.org/10.1177/1358863X12448457

13. Christakos S, Dhawan P, Verstuyf A, Verlinden L and Carmeliet G. Vitamin D: Metabolism, molecular mechanism of action, and pleiotropic effects. Physiol Rev. 2016;96(1):365-408.

14. Rosen CJ, Adams JS, Bikle DD, Black DM, Demay MB, Manson JE, et al. The nonskelet al effects of Vitamin D: An endocrine society scientific statement. Endocr Rev. 2012;33(3):456-492.

    https://doi.org/10.1210/er.2012-1000

15. Stricker H, Bianda FT, Guidicelli-Nicolosi S, Limoni C and Colucci G. Effect of a single, oral, high-dose Vitamin D supplementation on endothelial function in patients with peripheral arterial disease: A randomised controlled pilot study. Eur J VascEndovasc Surg. 2012;44(3):307-312.

    https://doi.org/10.1016/j.ejvs.2012.06.023

16. Van de Luijtgaarden KM, Voûte MT, Hoeks SE, Bakker EJ, Chonchol M, Stolker RJ, et al. Vitamin D deficiency may be an independent risk factor for arterial disease. Eur J VascEndovasc Surg. 2012;44(3):301-306.

17. Bonatto S, Paniz VM, Dutra CD, Henn RL. Vitamin D serum levels and peripheral arterial disease among Southern Brazilian adults. Rev AssocMéd Bras. 2020;66(3):268-274.

    https://doi.org/10.1590/1806-9282.66.3.268

18. Yuan J, Jia P, Hua L, Xin Z, Yang JK. Vitamin D deficiency is associated with risk of developingperipheral arterial disease in Type 2 diabetic patients. BMC CardiovascDisord. 2019;19(1):145.

    https://doi.org/10.1186/s12872-019-1125-0

19. Satilmis S, Celik O, Biyik I, Ozturk D, Celik KA, Akın F, et al. Association between serum Vitamin D levels and subclinical coronary atherosclerosis and plaque burden/composition in young adult population. Bosn J Basic Med Sci. 2015;15(1):67.

    https://doi.org/10.17305/bjbms.2015.238

20. Slinin Y, Foley RN, Collins AJ. Calcium, phosphorus, parathyroid hormone, and cardiovascular disease in hemodialysis patients: The USRDS waves 1, 3, and 4 study. J Am SocNephrol. 2005;16(6):1788-1793.

    https://doi.org/10.1681/ASN.2004040275

21. Kiernan TJ, O'Flynn AM, McDermott JH and Kearney P. Primary hyperparathyroidism and the cardiovascular system. Int J Cardiol. 2006;113(3):E89-E92.

    https://doi.org/10.1016/j.ijcard.2006.05.033

22. Trivedi DP, Doll R and Khaw KT. Effect of four monthly oral Vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: Randomised double blind controlled trial. BMJ. 2003;326(7387):469.

    https://doi.org/10.1136/bmj.326.7387.469

23. Avenell A, MacLennan GS, Jenkinson DJ, McPherson GC, McDonald AM, Pant PR, et al. Long-term follow-up for mortality and cancer in a randomized placebo-controlled trial of Vitamin D3 and/or calcium (RECORD trial). J ClinEndocrinolMetab. 2012;97(2):614-622.

    https://doi.org/10.1210/jc.2011-1309

24. Elamin MB, Abu Elnour NO, Elamin KB, Fatourechi MM, Alkatib AA, Almandoz JP, et al. Vitamin D and cardiovascular outcomes: A systematic review and meta-analysis. J ClinEndocrinolMetab. 2011;96(7):1931-1942.

    https://doi.org/10.1210/jc.2011-0398

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PS- Concept and design no study and coordination and revision of the manuscript; **SK-** Coordination, preparation, and revision of the manuscript; **KB-** Preparation and revision of manuscript; **AJ-** Biochemical analysis, preparation of manuscript, and revision of the manuscript; and **AT-** Literature review, manuscript preparation, revision of manuscript, data collection and statistical analysis, and prepared first draft of manuscript.

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