Original Article

DOI: 10.7860/JCDR/2024/65406.18966

Internal Medicine Section

# Vitamin D Status and its Correlation with Carotid Intima-media Thickness amongst Type 2 Diabetes Mellitus Patients: A Hospital-based Cross-sectional Study

SUBRAT KUMAR DUTTA[1], MAMATA SINGH[2], PRAMOD KUMAR ROUT[3], NIHAR RANJAN MOHANTY[4], ANURAG CHOUDHURY[5], BHAGYASHREE PANDA[6], BIBHU PADA HOTA[7], PRAVAT KUMAR THATOI[8]



## ABSTRACT

**Introduction:** There is rising concern about vitamin D deficiency around the globe due to its increasing association with multiple medical disorders. Diabetes Mellitus (DM) is an established risk factor for atherosclerotic disorders, and Carotid Artery Intima-Media Thickness (CIMT) is considered a radiological marker of subclinical atherosclerosis.

**Aim:** To find a correlation between serum 25-hydroxy vitamin D (25-(OH)-D) levels and CIMT among patients with DM.

**Materials and Methods:** A hospital-based cross-sectional study was conducted, including 100 adult patients with Type 2 DM who were admitted to the Department of Medicine at SCB Medical College and Hospital in Cuttack, Odisha, India from October 2020 to September 2021. Vitamin D deficiency was defined as serum 25-(OH)-D levels <20 ng/mL, and insufficiency as <30 ng/mL. The demographic profile of patients, family history of Type 2 DM, smoking history, blood pressure, haemogram, blood sugar, serum electrolytes, and lipid profile were studied. CIMT of the bilateral Common Carotid Artery (CCA) was measured by B-mode ultrasonography. CIMT values ≥ 0.8 mm were considered abnormal. Data were analysed using appropriate statistical tests in Statistical Packages for Social Sciences (SPSS) version 26.0.

**Results:** The present study included 55% males (n=55) and 45% females (n=45). The average age of the patients was 60 ±10 years, ranging from 26-75 years. Vitamin D deficiency was highly prevalent among patients with Type 2 DM (73% deficient, 12.5 ng/mL; 21% insufficient, 24.7 ng/mL). Vitamin D deficiency/insufficiency was higher among male participants (57.5%, 62%) compared to females (42.4%, 38%). Vitamin D levels were significantly associated with dyslipidemia. Mean CIMT among the vitamin D deficiency versus insufficiency versus normal group were 0.87 versus 0.87 versus 0.7 mm on the right Common Carotid Artery (CCA), and 0.95 versus 0.86 versus 0.75 mm on the left CCA, respectively. Significant negative correlations were observed for HbA1c (r=-0.025), Triglycerides (r=-0.274), right CIMT (r=-0.284), and left CIMT (r=-0.264) with serum 25-(OH)-D levels.

**Conclusion:** The majority of patients with Type 2 DM have concurrent vitamin D deficiency. A significant inverse linear association between serum vitamin D levels and CIMT was observed, indicating the association of vitamin D deficiency with subclinical atherosclerosis. Although unproven in the present study, the role of vitamin D supplementation in the improvement of atherosclerosis remains unclear.

**Keywords:** Atherogenesis, Cholecalciferol, Dyslipidemia, Prevalence, Ultrasonography

## INTRODUCTION

Vitamin D, a fat-soluble vitamin and immunomodulatory hormone, is well-known for its functions beyond calcium and bone homeostasis. The expression of Vitamin D Receptor (VDR) on immune cells has demonstrated the pathophysiology of vitamin D in several inflammatory conditions like DM, Systemic Lupus Erythematosus (SLE), Rheumatoid Arthritis, Asthma, Coronavirus Disease-2019 (COVID-19), etc. [1-4]. In recent years, vitamin D deficiency has become an epidemic worldwide, affecting individuals of all ages, genders, and ethnicities [5]. In India, the prevalence of vitamin D deficiency in the community ranges from 50-94% [6,7], and among patients with DM, it is reported to be 63-91% [8,9], which is an established risk factor for atherosclerosis [10].

While carotid angiography is considered the gold standard for demonstrating atherosclerosis, its invasiveness and cost limit its routine use [10]. An alternative non invasive modality is the measurement of CIMT using B-mode ultrasonography, which is considered an accessible surrogate marker of atherosclerosis [9,10].

Several international studies, along with a few conducted in India, have been carried out to establish the role of vitamin D in atherosclerosis by measuring CIMT levels [11-15]. However, only one study focused on Type 2 DM patients in India [9]. Among patients with Type 1 DM, only 8% had normal vitamin D status, and there was no significant association between vitamin D deficiency and higher CIMT levels [15]. A recent study involving the Brazilian population descended from African slaves reported a low prevalence of vitamin D deficiency (4.8%), and no independent association was observed between vitamin D levels and CIMT [16]. A similar study on Korean adults found that low vitamin D levels were not associated with higher CIMT but showed a significant negative correlation with carotid atherosclerosis [17]. Furthermore, the association of dyslipidemia with vitamin D deficiency and the role of vitamin D supplementation in atherosclerosis remain controversial [18,19]. Despite multiple studies conducted globally, a uniform result on vitamin D status and subclinical atherosclerosis has yet to be achieved. Given the scarcity of studies assessing vitamin D levels and CIMT among diabetics in India [9,20], the present study aimed to estimate the prevalence of vitamin D deficiency among Type 2 DM patients and correlate it with their CIMT levels.

## MATERIALS AND METHODS

A cross-sectional study was conducted, including 100 adult patients with Type 2 DM who were admitted to the Department of Medicine at SCB Medical College and Hospital in Cuttack, Odisha. The study was carried out over a period of one year, from

October 2020 to September 2021. Written informed consent was obtained from all study participants in the local Odia language. The study protocol was approved by the Institutional review board and Ethical Committee (letter no. IEC 204/26.08.2020).

**Sample size calculation:** The sample size was calculated to be 83, based on a prevalence of vitamin D deficiency among diabetics of 71% and a margin of error of 10% [9]. However, the final sample size included in the study was 100.

**Inclusion criteria:** Patients of age ≥18 years with a diagnosis of Type 2 DM or under treatment for Type 2 DM were included in the study.

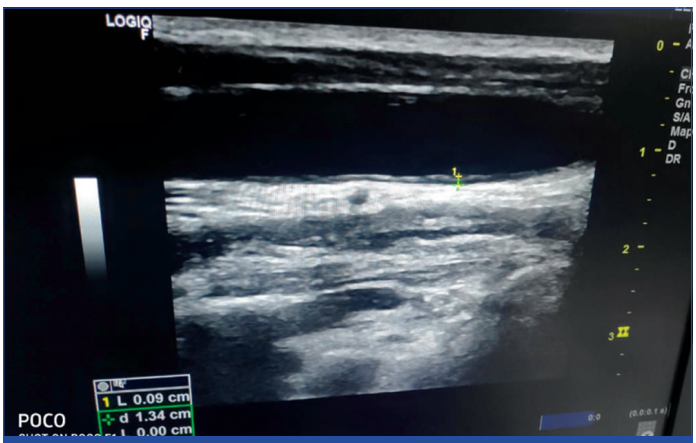
**Exclusion criteria:** Patients diagnosed with Type 1 DM, Gestational DM, diabetic ketoacidosis, or hyperosmolar hyperglycemic state, those with a recent history of acute illness, chronic kidney disease, chronic liver disease, patients taking medications likely to affect vitamin D levels (such as calcium and vitamin D supplements, Teriparatide injections, thyroxine, anticonvulsants, orlistat, cholestyramine), pregnant individuals, known patients with cardiovascular diseases, dyslipidemia, and chronic diarrhoea were excluded from the study.

### Study Procedure

A detailed history, thorough physical and clinical examination, and medication history were obtained from each patient. Blood pressure was measured twice, with a five-minute apart using an automated digital blood pressure machine, and the mean value was recorded. Participants were subjected to eight hours overnight fasting, and blood samples were collected for routine investigations including complete blood count, serum fasting blood sugar, two-hour post-prandial blood sugar, serum C-peptide, serum electrolytes, kidney function tests, liver function tests, lipid profile, HbA1c, and urine routine microscopy.

Vitamin D (serum 25-(OH)-D) levels were measured using a competitive Enzyme-linked Immunosorbent Assay (ELISA) kit manufactured by Euro-Immune (Germany). The participants were divided into three groups based on their serum 25-(OH)-D levels: >30 ng/mL as normal, 20-30 ng/mL as insufficient, and <20 ng/mL as deficient [6].

The CIMT was measured using B-mode ultrasonography. A B-mode image was taken at the distal Common Carotid Artery (CCA). The patient's head was rotated 45° away from the imaged side, and the probe was held parallel to the artery to ensure clear visualisation of the double lines of the lumen-intima and media-adventitia interfaces on both near and far walls. The CIMT measurement was taken below the bulb and extended caudally over a distance of approximately 1 cm [Table/Fig-1]. CIMT ≥0.8 mm was considered abnormal [12].




**[Table/Fig-1]:** Carotid Intima-Media Thickness (CIMT) measured by B mode ultrasonography.

## STATISTICAL ANALYSIS

The data were entered in Microsoft Excel, and statistical analysis was performed using IBM SPSS version 26.0. The data were checked for normality. Normally distributed continuous data were presented as mean±Standard Deviation (SD), while categorical data were presented as proportions. Differences between groups were assessed using one-way Analysis of Variance (ANOVA) for continuous variables and the Chi-square test for categorical variables. Pearson's correlation was used to analyse the relationship between different parameters, including CIMT (right) and CIMT (left), with serum vitamin D levels. The correlation coefficient (r) was reported. A p-value of less than 0.05 was considered significant, while a p-value of less than 0.001 was considered highly significant. A scatter plot of vitamin D levels and CIMT was created using Microsoft Excel.

## RESULTS

The present study included 100 patients, comprising 55% males (n=55) and 45% females (n=45). The average age of the patients was 60 ±10 years, with an age range of 26 to 75 years. [Table/Fig-2] demonstrates that the prevalence of vitamin D deficiency was 73% in the current study, with a mean serum 25-(OH)-D level of 12.5 ng/mL, while 21% were insufficient, with a mean serum 25-(OH)-D level of 24.7 ng/mL. Male patients exhibited severe vitamin D deficiency (57.5%) or insufficiency (62%) compared to female patients (42.5% and 38%, respectively).

| Variables | Vitamin D levels (Mean±SD) | | | p-value |
|---|---|---|---|---|
| | Deficient (n=73) | Insufficient (n=21) | Normal (n=6) | |
| Age (years) | 58.8±11.6 | 63.7±7.8 | 62.7±5.9 | 0.155 |
| Gender (male/female) | 42 (57.5)/31 (42.5) | 13 (62)/8 (38) | 0/6 (100) | 0.019 |
| BMI (kg/m$^2$) | 24.09±2.1 | 25.6±1.6 | 25.5±2.05 | 0.006 |
| Family history (n/%) | 43 (58.9) | 21 (100) | 6 (100) | <0.001 |
| Smoking (n/%) | 11 (15.1) | 2 (9.5) | 0 | 0.497 |
| Antihypertensive use | 15 (20.5) | 4 (19) | 0 | 0.467 |
| SBP (mmHg) | 121.3±9.5 | 122.4±12.3 | 127.7±14.1 | 0.353 |
| DBP (mmHg) | 77.4±6.4 | 73.4±5.1 | 75.3±6.3 | 0.036 |
| Hb (g%) | 10±1.3 | 10.6±0.7 | 9.9±1.4 | 0.169 |
| TLC (cells/mm$^3$) | 7339±1498 | 7100±1360 | 7366±950 | 0.793 |
| ESR (mm) | 20.6±6.8 | 20.8±12.06 | 16.3±4.5 | 0.447 |
| FBS (mg/dL) | 169.6±42.8 | 152.8±20.4 | 165.8±52.2 | 0.237 |
| 2 hour-PPBS | 247.6±53.4 | 218.3±18.6 | 262.7±75.8 | 0.039 |
| HbAIC (g%) | 7.5±0.6 | 7.3±0.5 | 7.03±0.7 | 0.194 |
| Sodium (mEq/L) | 139.9±4.7 | 139±4.8 | 140.6±3.4 | 0.689 |
| Potassium (mEq/L) | 3.8±0.4 | 3.9±0.5 | 4.2±0.3 | 0.031 |
| HDL (mg/dL) | 44.1±9 | 43±9.6 | 47.5±9.2 | 0.570 |
| LDL (mg/dL) | 132.7±32.1 | 126.8±31.4 | 129±39.6 | 0.755 |
| TG (mg/dL) | 112.7±17.1 | 99±20.7 | 97.3±22.8 | 0.004 |
| Vitamin D (ng/mL) | 12.5±3.8 | 24.7±2.8 | 38±9.8 | <0.001 |
| CIMT (mm) (R) | 0.87±0.16 | 0.87±0.2 | 0.7±0.2 | 0.047 |
| CIMT (mm) (L) | 0.95±0.21 | 0.86±0.2 | 0.75±0.1 | 0.029 |

**[Table/Fig-2]:** Demographic, laboratory, and radiological parameters compared with respect to different serum vitamin D levels.
*BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; Hb: Haemoglobin; TLC: Total leukocyte count; ESR: Erythrocyte sedimentation rate; FBS: Fasting blood sugar; PPBS: Postprandial blood sugar; HbA1c: Haemoglobin A1c; HDL: High density lipoprotein; LDL: Low density lipoprotein; TG: Triglyceride; CIMT: Carotid intima-media thickness; One-way ANOVA test; Chi-square test

The majority of participants in the vitamin D deficient group had a positive family history of Type 2 DM, smoking, and antihypertensive drug use, as opposed to the insufficient and normal vitamin D groups. Smoking history was present in 13% of the patients (n=13).

Diastolic Blood Pressure (DBP) values significantly differed among vitamin D deficient, insufficient, and normal vitamin D groups (77.4 mmHg versus 73.4 mmHg versus 75.3 mmHg, p=0.036). The average 2 hour-Postprandial Blood Sugar (PPBS) in the deficient group was 247.6 mg/dL, compared to 218.3 mg/dL in the

insufficient group (p=0.039). Furthermore, the serum TG levels were 112.7 mg/dL in the vitamin D deficient group and 99 mg/dL in the insufficient group (p=0.004).

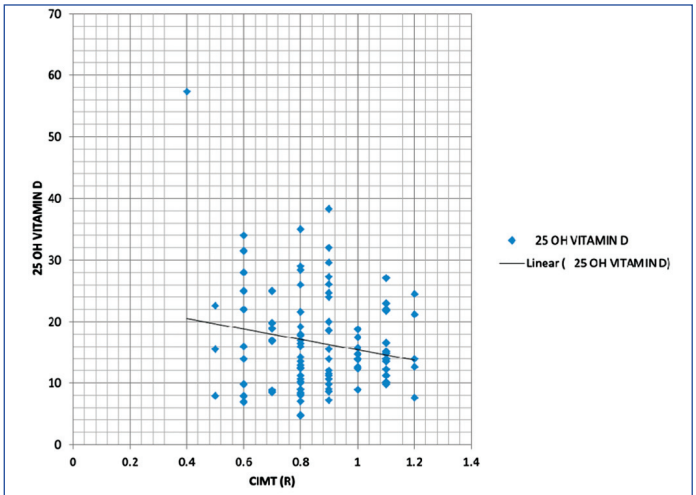
Regarding CIMT, 8% of patients had normal CIMT, while 92% had abnormal CIMT in either carotid artery. CIMT (R) measured 0.87±0.16 mm in the vitamin D deficient group, 0.87±0.2 mm in the insufficient group, and 0.7±0.2 mm in the normal vitamin D group (p<0.05). Similarly, CIMT (L) was 0.95±0.21 mm in the deficient group, 0.86±0.2 mm in the insufficient group, and 0.75±0.1 mm in the normal vitamin D group (p<0.05).

[Table/Fig-3] presents correlations between various parameters, including CIMT (R) and CIMT (L), with vitamin D levels. Age, BMI, and serum potassium positively correlated with vitamin D levels, with Pearson's correlation coefficients (r) of 0.247 (p-value 0.013), 0.358 (p-value <0.001), and 0.315 (p-value 0.001), respectively. Conversely, HbA1c, serum TG, CIMT (R), and CIMT (L) correlated negative correlations with vitamin D levels, with Pearson's correlation coefficients (r) of -0.025 (p-value 0.012), -0.274 (p-value 0.006), -0.284 (p-value 0.005), and -0.264 (p-value 0.008), respectively.

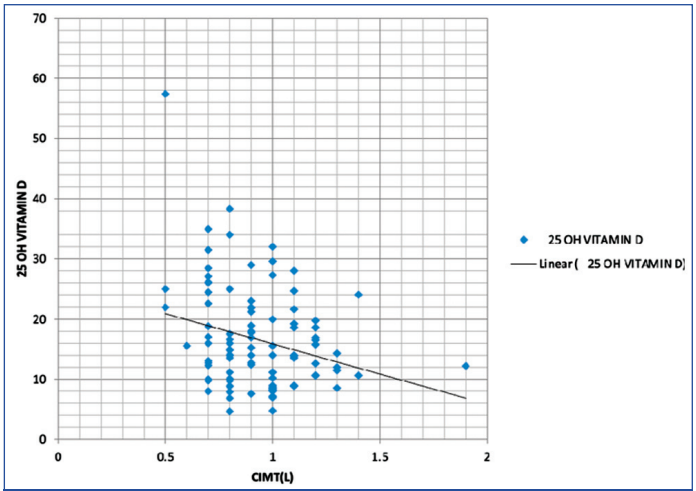
[Table/Fig-4,5] graphically illustrate the linear increase in CIMT with decreasing serum vitamin D levels.

| Parameters | Vitamin D (Pearson's correlation coefficient, r) | p-value |
|---|---|---|
| Age (in years) | 0.247 | 0.013 |
| BMI (kg/m$^2$) | 0.358 | <0.001 |
| SBP (mmHg) | 0.107 | 0.29 |
| DBP (mmHg) | -0.148 | 0.141 |
| Hb (g%) | 0.109 | 0.28 |
| TLC (cells/mm$^3$) | -0.172 | 0.087 |
| ESR (mm) | -0.105 | 0.3 |
| FBS (mg/dL) | -0.18 | 0.073 |
| 2 hour-PPBS | -0.028 | 0.779 |
| HbA1c (g%) | -0.025 | 0.012 |
| Sodium (mEq/L) | -0.034 | 0.734 |
| Potassium (mEq/L) | 0.315 | 0.001 |
| HDL (mg/dL) | -0.003 | 0.976 |
| LDL (mg/dL) | -0.095 | 0.346 |
| TG (mg/dL) | -0.274 | 0.006 |
| CIMT (mm) (R) | -0.284 | 0.005 |
| CIMT (mm) (L) | -0.264 | 0.008 |

**[Table/Fig-3]:** Correlation of different parameters with serum vitamin D levels.
p<0.05 statistically significant, p<0.001 statistically highly significant




**[Table/Fig-4]:** Scatter plot demonstrating CIMT (R) and serum vitamin D levels.




**[Table/Fig-5]:** Scatter plot demonstrating CIMT (L) and serum vitamin D levels.

## DISCUSSION

There is a rising concern regarding vitamin D deficiency due to its association with multiple medical disorders, with prevalence ranging from 50-94% in India [6,7]. The prevalence of vitamin D deficiency reported in the present study (73%) aligns with other Indian studies (71% and 81%) [9,11]. DM is an established risk factor for atherosclerotic diseases like coronary artery disease and cerebrovascular accidents. Vitamin D deficiency is prevalent among diabetics, often exacerbating atherosclerotic diseases due to its involvement in inflammation, endothelial dysfunction, and immune cell recruitment [21]. As carotid angiography is an invasive modality for diagnosing atherosclerosis, the measurement of CIMT using ultrasonography serves as an accessible and non invasive alternative [19].

The present study reveals a significant inverse relationship between vitamin D levels and CIMT, consistent with similar studies in different regions of India [9,11,12,22], and clinical studies [13,23-26] and meta-analyses [19,27,28] conducted globally. An inverse correlation between vitamin D and CIMT was also observed among Type 1 DM patients, although it did not reach statistical significance [15]. Similar findings were observed in another study involving the Brazilian population descended from African slaves [16]. However, Choi YK et al., found no significant association between vitamin D status and CIMT but noted a significant negative correlation with carotid atherosclerosis, as measured by the presence of carotid plaques [17].

In the present study, the majority of patients with vitamin D deficiency and insufficiency were males, in line with the study by Mulatkar CP et al., (males, 54%) [9]. Furthermore, Subramanian A et al., reported that diabetic males had significantly lower serum vitamin D concentrations compared to diabetic females (9.07 versus 12.6 ng/mL) [29].

According to Mantha S et al., the relative contribution to CIMT was maximum for smoking (41%), followed by the total cholesterol HDL ratio (34%) and vitamin D deficiency (25%) [11]. Although 1 in 10 patients reported a history of smoking in the present study, it was not statistically significant among the deficient and insufficient groups. This finding aligns with the study by Wang Y and Zhang H [24].

Dyslipidemia was associated with vitamin D deficiency, although there are inconsistent results regarding the particular type of cholesterol molecule involved. Some studies show an association with LDL-cholesterol, while in others, neither total cholesterol nor HDL-cholesterol nor triglycerides were associated [17,19,24]. In the present study, a higher Triglyceride (TG) level was significantly associated with vitamin D deficiency.

Similar inconclusive findings were observed for both Systolic Blood Pressure (SBP) and DBP. Choi YK et al., reported a significant difference in DBP (vitamin D deficient versus non deficient: 80.3 versus 74.6 mmHg), similar to the results in the current study [17].

However, neither DBP nor SBP values were statistically significant among the vitamin D deficient groups in the study by Wang Y and Zhang H [24].

According to Surdu AM et al., an inverse correlation was observed between vitamin D levels and serum total cholesterol, LDL, and triglyceride levels, whereas HDL levels correlated positively with vitamin D levels [18]. Additionally, vitamin D supplementation in different dosages improved lipid parameters [18]. However, supplementing Type 2 DM patients with vitamin D demonstrated a reduction in total cholesterol content within the monocytes, without affecting serum triglycerides, LDL cholesterol, and HDL cholesterol [18]. Unlike other studies, present study demonstrated a negative correlation of all the lipid parameters with vitamin D levels.

Multiple randomised clinical trials and systematic reviews extend the controversy surrounding low-dose vitamin D supplementation, showing no effect on myocardial infarction, stroke, hyperlipidemia, insulin resistance, blood pressure, and, consequently, cardiovascular mortality [18,30]. However, another randomised clinical trial demonstrated that vitamin D supplementation, along with vitamin K and calcium, for diabetic patients with coronary artery disease had beneficial effects on CIMT [30]. In addition to the inconsistencies in reports on vitamin D supplementation and atherosclerosis, some studies have reported that vitamin D deficiency is not independently associated with subclinical atherosclerosis among patients with SLE or non diabetic HIV patients [31,32]. Although vitamin D plays a significant role in multiple pathophysiological mechanisms involving infection, inflammation, and autoimmunity, there is a lack of consensus regarding its involvement in atherosclerosis.

### Limitation(s)

The present study did not evaluate the vitamin D status in patients with diabetic ketoacidosis and Hyperosmolar hyperglycaemic state, which are extreme complications of Type 2 DM. Although patients receiving Teriparatide injections (recombinant parathyroid hormone) for osteoporosis were excluded, parathyroid hormone or serum calcium was not measured due to financial limitations. Furthermore, the present study did not evaluate the effect of vitamin D supplementation on CIMT. Conducting cohort or case-control studies to determine the cause-and-effect relationship between vitamin D and atherosclerosis is recommended. Additionally, multiple randomised clinical trials are recommended to estimate the effect of vitamin D supplementation on atherosclerosis.

## CONCLUSION(S)

The present study reports a high prevalence of vitamin D deficiency among patients with Type 2 DM. Male sex and patients with a family history of Type 2 Diabetes are commonly affected. Dyslipidemia is significantly associated with vitamin D deficiency. A significant inverse linear association was observed between vitamin D levels and CIMT, indicating its association with sub-clinical atherosclerosis. Although unproven in the present study, the effect of vitamin D supplementation on the improvement in atherosclerosis remains unclear. Hence, future studies are recommended for further evaluation of vitamin D supplementation in atherosclerosis.

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**PARTICULARS OF CONTRIBUTORS:**
1. Senior Resident, Department of Clinical Immunology and Rheumatology, SCB Medical College and Hospital, Cuttack, Odisha, India.
2. Professor, Department of Radiodiagnosis, Jajati Keshari Medical College and Hospital, Jajpur, Odisha, India.
3. Associate Professor, Department of General Medicine, Dharanidhar Medical College, Keonjhar, Odisha, India.
4. Assistant Professor, Department of General Medicine, KIMS and PBMH Hospital, Bhubaneswar, Odisha, India.
5. General Duty Medical Officer, Department of Emergency Department, NTPC Hospital, Kaniha, Talcher, Odisha, India.
6. Assistant Professor, Department of General Medicine, PRM Medical College and Hospital, Baripada, Odisha, India.
7. Assistant Professor, Department of General Medicine, Dharanidhar Medical College, Keonjhar, Odisha, India.
8. Professor, Department of General Medicine, Dharanidhar Medical College, Keonjhar, Odisha, India.

**NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:**
Pravat Kumar Thatoi,
Flat-2C, Kingston Residency, Cantonment Road, Cuttack-753001, Odisha, India.
E-mail: drpravatthatoi@yahoo.co.in

**PLAGIARISM CHECKING METHODS:** [Jain H et al.]
- Plagiarism X-checker: May 17, 2023
- Manual Googling: Sep 13, 2023
- iThenticate Software: Oct 07, 2023 (10%)

**ETYMOLOGY:** Author Origin

**EMENDATIONS:** 7

**AUTHOR DECLARATION:**
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **May 13, 2023**
Date of Peer Review: **Aug 04, 2023**
Date of Acceptance: **Oct 11, 2023**
Date of Publishing: **Jan 01, 2024**