

Correlation of Inflammatory Marker and Vitamin D Level with Carotid Intima Media Thickening in Pre-Diabetes

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Abstract: ***Introduction:** Inflammatory markers (ESR, CRP, IL - 6 and NLR) are increased as the CIMT increases suggesting the role of inflammatory markers in pathogenesis of atherosclerosis in prediabetics. **Aims and Objectives:** To find the correlation of inflammatory markers, vitamin D levels with CIMT in prediabetes. **Methods:** The study type is cross sectional study. The work was conducted in Department of Medicine, M. L. B. Medical College, Jhansi. A sample size of 200 patients attending Medicine OPD/IPD and Diabetic OPD were selected as per criteria. **Results:** In our study 78 out of 100 prediabetics had low Vitamin D level, 66 had raised CRP level, 68 had raised ESR level, 68 had raised IL - 6 level, 67 had Vitamin D < 30 and CIMT > 0.88. **Conclusion:** Evaluation of inflammatory markers, vitamin D level and measurement of CIMT in pre diabetics can serve as an early marker of atherosclerosis, allowing physicians to plan early interventions to decrease future cardiovascular disease risk.*

Keywords: prediabetics, inflammatory markers, CIMT, Vitamin D

1. Introduction

Type 2 DM is a complex disease in which both genetic and environmental factors interact in determining impaired beta cell insulin secretion and peripheral insulin resistance. One of the hallmarks of T2DM is low grade inflammation resulting in rise in circulating cytokine such as CRP (C - reactive protein), ESR (erythrocyte sedimentation rate), IL - 6 (interleukin - 6).

Prediabetes is a state of elevated plasma glucose in which the threshold for diabetes has not yet been reached and can predispose to the development of type 2 diabetes, cardiovascular diseases and also many diseases. The prevalence of prediabetes in India is 14%. The development of atherosclerosis begins with prediabetes. The length of asymptomatic period in prediabetes exposes patient to cardiovascular risk factors and increases the risk of coronary artery disease; therefore, early diagnosis and prevention through appropriate screening is important. Thus, CIMT come into role.

CIMT is increased in Diabetes and has also seen to be increased in Prediabetes. It has also been seen that Vit - D level decreased in both Diabetes and Prediabetes.

2. Aims and Objectives

- 1) To find the association of inflammatory markers with CIMT in pre diabetes.
- 2) To find association of neutrophil to lymphocytes ratio and CIMT in pre diabetes.
- 3) To find the correlation of inflammatory markers, vitamin D levels with CIMT in pre diabetes.

3. Material and Methods

The study type is cross sectional study. The work was conducted in Department of Medicine, M. L. B. Medical College, Jhansi. A sample size of 200 patients attending Medicine OPD/IPD and Diabetic OPD were selected as per criteria.

A pre - structured Proforma was filled up for the study. Each subject was given a thorough work up for history and physical examination to fulfill the inclusion and exclusion criteria. Routine haematological and biochemical investigations were carried out. The following parameters were measured at the time of enrolment into the study:

Inclusion Criteria:

Patients of prediabetes, defined as

Fasting plasma glucose: 6.0 - 6.9mmol/l (100 - 125mg/dl)

or

2hour plasma glucose: 7.8 - 11.0mmol/l (140 - 200mg/dl)

or

Hba1c: 5.7 - 6.4%

Exclusion Criteria:

- Subjects who received vitamin D or calcium supplementation in the previous 6 months.
- Pregnancy
- Severe end - organ damage
- Malignancy
- Known diabetes mellitus and
- Other endocrine disorders
- Patient not willing to be enrolled in the study.

Volume 12 Issue 5, May 2023

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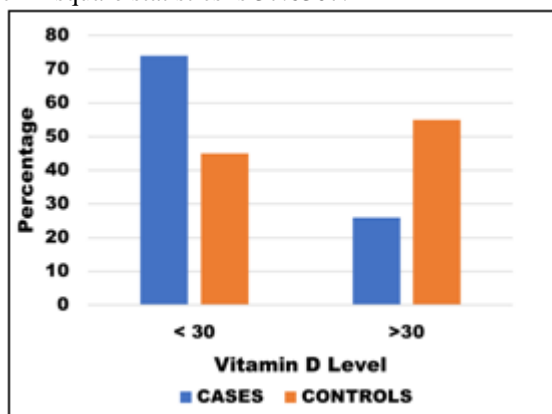
4. Results

The present study was conducted in the department of Medicine, MLB Medical college Jhansi, on 200 patients admitted to our hospital, out of which 100 were cases (Prediabetic) as per criteria set in material and methods and remaining 100 were controls who were equally matched according to age, sex, education and risk factors.

Table 1: Distribution According to Vitamin D Level

Vit. D level	Case (%)	Controls (%)	p Value
< 30	74 (74%)	45 (45%)	< 0.00001
>30	26 (26%)	55 (55%)	
Total	100 (100%)	100 (100%)	

The chi - square statistics is 37.6307.

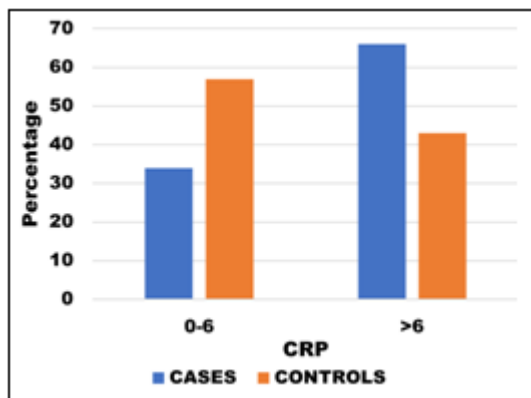


Out of 100 cases 74 patients (74 %) had Vitamin D level < 30 and 26 patients (26 %) had level > 30. Out of 100 controls 45 patients (45 %) had vitamin D level < 30 and 55 patients (55 %) had level > 30. As evident from the above table, prevalence of vitamin D deficiency is more in pre diabetics and is statistically significant (p Value<0.0001).

Table 2: Distribution According To CRP

CRP	Case (%)	Controls (%)	p Value
0 - 6	34 (34 %)	57 (57 %)	0.001091
>6	66 (66 %)	43 (43 %)	
Total	100 (100%)	100 (100%)	

The chi - square statistics is 10.6664.



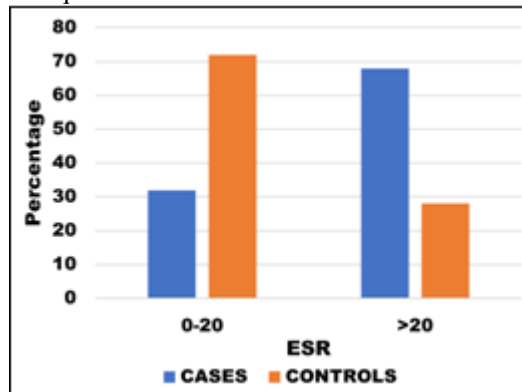
Out of 100 cases 34 patients (34 %) had CRP level between 0 to 6 and 66 patients (66 %) had level > 6. Out of 100 controls 57 patients (57 %) had CRP level between 0 to 6 and 43 patients (43 %) had level > 6. As evident from the

above table CRP level was increased more in pre diabetics than normal population and is statistically significant (p Value - 0.001).

Table 3: Distribution according to ESR

ESR	Case (%)	Controls (%)	p Value
0 - 20	32 (32 %)	72 (72 %)	<0.0001
>20	68 (68 %)	28 (28 %)	
Total	100 (100 %)	100 (100 %)	

The chi - square statistics is 32.0513.



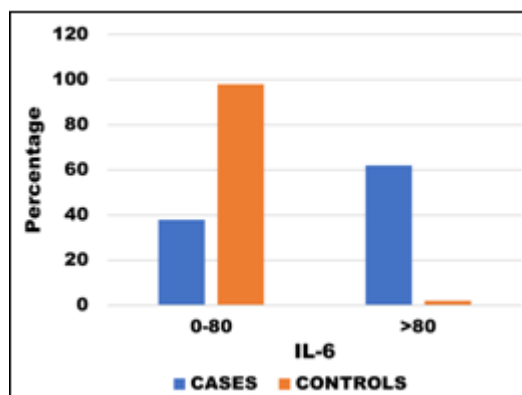
Out of 100 cases 32 patients (32 %) had ESR level between 0 to 20 and 68 patients (68 %) had level > 20. Out of 100 controls 72 patients (72 %) had ESR level between 0 to 20 and 28 patients (28 %) had level > 20. As evident from the above table ESR level was increased more in pre diabetics than normal population and is statistically significant (p Value<0.0001).

Table 4: Distribution according to IL - 6

IL - 6	Case (%)	Controls (%)	p Value
0 - 80	38 (38 %)	98 (98 %)	<0.0001
>80	62 (62 %)	2 (2 %)	
Total	100 (100 %)	100 (100 %)	

The chi - square statistics is 41.3603.

*IL - 6 value in normal population (control group) is taken from reference population value as stated in study by Dan q et al (4)



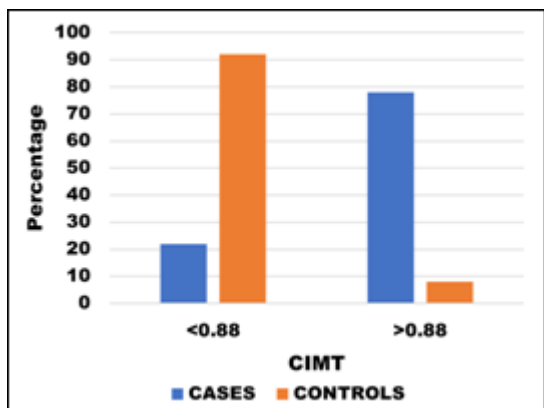
Out of 100 cases 38 patients (38 %) had IL - 6 level between 0 to 80 and 62 patients (62 %) had level > 80. Out of 100 controls 98 patients (98 %) had IL - 6 level between 0 to 80 and 2 patients (2 %) had level > 80. As evident from the above table IL - 6 level was increased more in pre diabetics

than normal population and is statistically significant (p Value<0.0001).

Table 5: Distribution according to CIMT levels

CIMT level	Case (%)	Control (%)	p Value
< 0.88	22 (22 %)	92 (92 %)	<0.00001
> 0.88	78 (78 %)	8 (8 %)	
Total	100 (100%)	100 (100 %)	

The chi - square statistics is 59.7091.

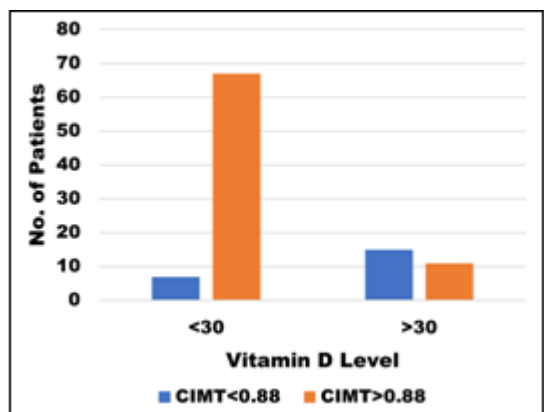


Out of 100 cases 22 patients (22 %) had CIMT level between < 0.88 and 78 patients (78 %) had level > 0.88. Out of 100 controls 92 patients (92 %) had CIMT level between < 0.88 and 8 patients (8 %) had level > 0.88. As evident from the above table CIMT level was more in pre diabetics than normal population and is statistically significant (p Value<0.0001).

Table 6 (a): Correlation of Vit D levels by CIMT in cases

Vit. D level	CIMT		p Value
	<0.88	>0.88	
< 30	7 (31.82%)	67 (85.9%)	<0.002496
>30	15 (68.18%)	11 (14.1%)	
Total	22 (100%)	78 (100%)	

The chi - square statistics is 16.4278.



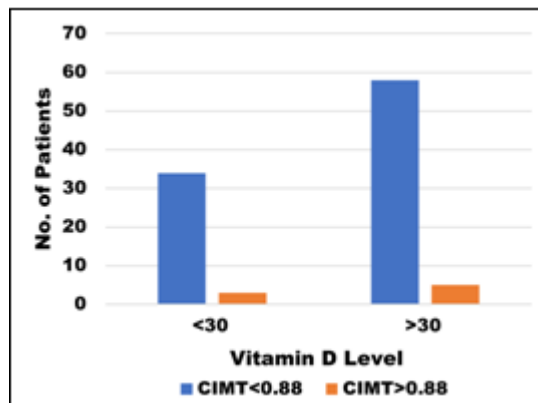
In 100 cases, 22 patients had CIMT level < 0.88 out of which 7 patients had Vitamin D level < 30 and 15 had Vitamin D level > 30. In 100 cases, 78 patients had CIMT level > 0.88 out of which 67 patients had Vitamin D level < 30 and 11 had Vitamin D level > 30. As evident from the above table, the patients who had increased CIMT level

were found to be more deficient for vitamin D and is statistically significant (p Value<0.002).

Table 6 (b): Correlation of Vit D levels by CIMT in controls

Vit. D level	CIMT		p Value
	<0.88	>0.88	
< 30	34 (36.96%)	3 (37.5%)	<0.00642
>30	58 (63.04%)	5 (62.50%)	
Total	92 (100%)	8 (100%)	

The chi - square statistics is 25.9934.



In 100 controls, 92 patients had CIMT level < 0.88 out of which 34 patients had Vitamin D level < 30 and 58 had Vitamin D level > 30. In 100 controls, 8 patients had CIMT level > 0.88 out of which 3 patients had Vitamin D level < 30 and 5 had Vitamin D level > 30. As evident from the above table, due to small sample size statistical significance could not be established but it is evident that there is negative correlation between vitamin D level and CIMT level in normal population.

Table 7 (a): Correlation of N/L ratio by CIMT in cases

N/L ratio	CIMT	
	<0.88	>0.88
Mean ± SD	1.314±2.568	3.36±2.406

High NLR ratio was seen in patients with CIMT level > 0.88.

Table 7 (b): Correlation of N/L ratio by CIMT in controls

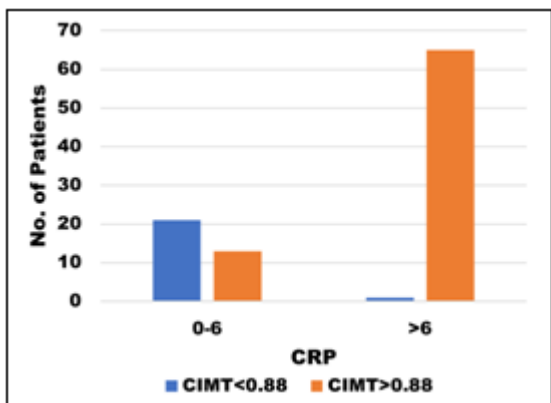
N/L ratio	CIMT	
	<0.88	>0.88
Mean ± SD	5.34±3.522	8.88±5.919

High NLR ratio was seen in patients with CIMT level > 0.88.

Table 8 (a): Correlation of CRP by CIMT in cases

CRP	CIMT		p Value
	<0.88	>0.88	
0 - 6	21 (95.45%)	13 (16.7%)	<0.001086
>6	1 (4.5%)	65 (83.3%)	
Total	22 (100%)	78 (100%)	

The chi - square statistics is 44.401.

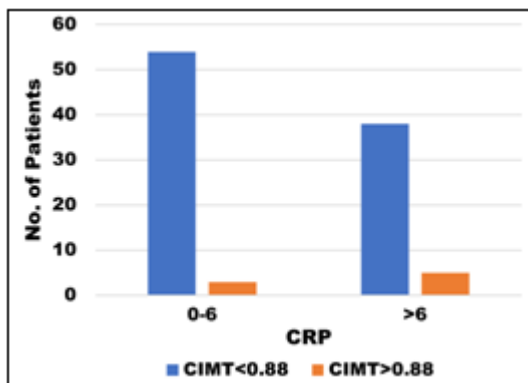


In 100 cases, 22 patients had CIMT level < 0.88 out of which 21 patients had CRP level between 0 to 6 and 1 had CRP level > 6. In 100 cases, 78 patients had CIMT level > 0.88 out of which 13 patients had CRP level between 0 to 6 and 65 had CRP level > 6. As evident from the above table, CRP level was high in patients who had CIMT level > 0.88 and is statistically significant (p Value<0.001).

Table 8 (b): Correlation of CRP by CIMT in control

CRP	CIMT		p Value
	<0.88	>0.88	
0 - 6	54 (58.7%)	3 (37.5%)	<0.00395
>6	38 (41.3%)	5 (62.5%)	
Total	92 (100%)	8 (100%)	

The chi - square statistics is 32.692.

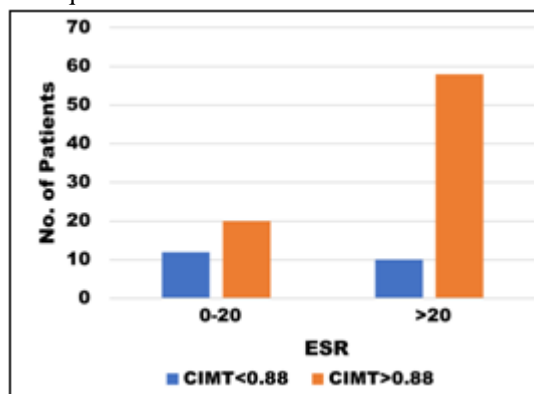


In 100 controls, 92 patients had CIMT level < 0.88 out of which 54 patients had CRP level between 0 to 6 and 38 had CRP level > 6. In 100 controls, 8 patients had CIMT level > 0.88 out of which 3 patients had CRP level between 0 to 6 and 5 had CRP level > 6. As evident from the above table, CRP level was high in patients who had CIMT level > 0.88 but due to small sample size statistical significance could not be established but it is evident that there is positive correlation between CRP level and CIMT level in normal population.

Table 9 (a): Correlation of ESR by CIMT in cases

ESR	CIMT		p Value
	<0.88	>0.88	
0 - 20	12 (54.55%)	20 (25.64%)	<0.000058
>20	10 (45.45%)	58 (74.36%)	
Total	22 (100%)	78 (100%)	

The chi - square statistics is 19.5211.

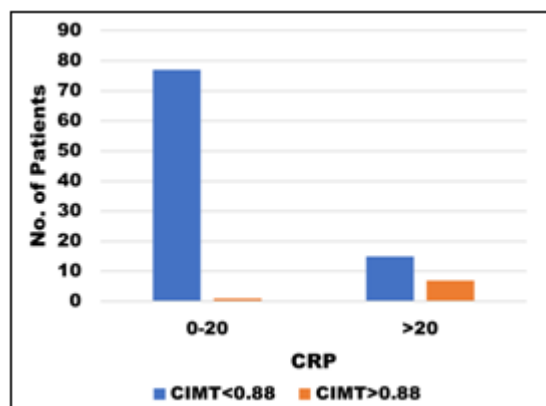


In 100 cases, 22 patients had CIMT level < 0.88 out of which 12 patients had ESR level between 0 to 20 and 10 had ESR level > 20. In 100 cases, 78 patients had CIMT level > 0.88 out of which 20 patients had ESR level between 0 to 20 and 58 had ESR level >20. As evident from the above table, ESR level was high in patients who had CIMT level > 0.88 and statistically significant (p Value 0.001)

Table 9 (b): Correlation of ESR by CIMT in control

ESR	CIMT		p Value
	<0.88	>0.88	
0 - 20	77 (83.7%)	1 (12.5%)	<0.002811
>20	15 (16.3%)	7 (87.5%)	
Total	92 (100%)	8 (100%)	

The chi - square statistics is 24.186

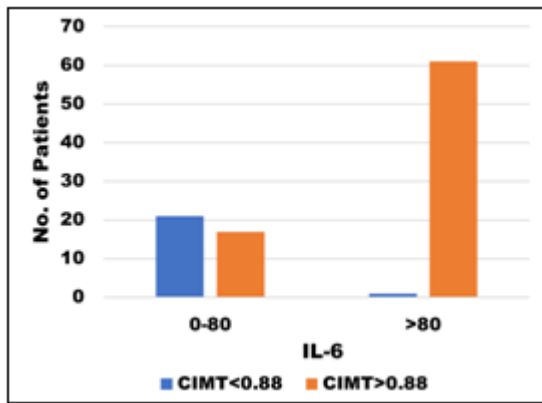


In 100 cases, 92 patients had CIMT level < 0.88 out of which 77 patients had ESR level between 0 to 20 and 15 had ESR level > 20. In 100 cases, 8 patients had CIMT level > 0.88 out of which 1 patient had ESR level between 0 to 20 and 7 had ESR level > 20. As evident from the above table, ESR level was high in patients who had CIMT level > 0.88 and statistically significant (p Value - 0.002).

Table 10 (a): Correlation of IL - 6 by CIMT in cases

IL - 6	CIMT		p Value
	<0.88	>0.88	
0 - 80	21 (95.46%)	17 (21.79%)	<0.00106
>80	1 (4.54%)	61 (78.21%)	
Total	22 (100%)	78 (100%)	

The chi - square statistics is 14.786.



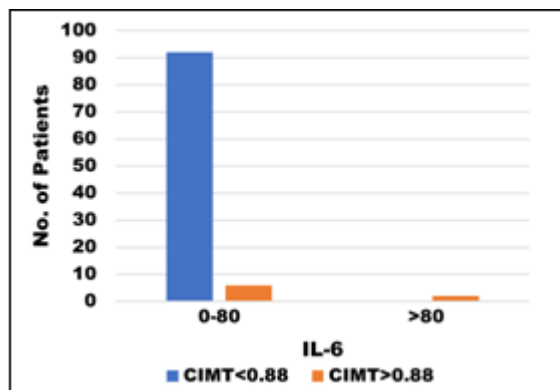
In 100 cases, 22 patients had CIMT level < 0.88 out of which 21 patients had IL - 6 level between 0 to 80 and 1 had IL - 6 level > 80. In 100 controls, 17 patients had CIMT level > 0.88 out of which 17 patients had IL - 6 level between 0 to 80 and 61 had IL - 6 level > 80. As evident from the above table, IL - 6 level was high in patients who had CIMT level > 0.88 and statistically significant (p Value - 0.001).

Table 10 (b): Correlation of IL - 6 by CIMT in control

IL - 6	CIMT		p Value
	<0.88	>0.88	
0 - 80	92 (100%)	6 (75%)	<0.0346
>80	0	2 (25%)	
Total	92 (100%)	8 (100%)	

The chi - square statistics is 13.5845

*IL - 6 value in normal population (control group) is taken from reference population value as stated in study by Dan q et al (4)



In 100 controls, 92 patients had CIMT level < 0.88 out of which all 92 patients had IL - 6 level between 0 to 80 and none had IL - 6 level > 80. In 100 controls, 8 patients had CIMT level > 0.88 out of which 6 patients had IL - 6 level between 0 to 80 and 2 had IL - 6 level > 80. As evident from the above table, IL - 6 level was high in patients who had CIMT level > 0.88 but due to small sample size statistical significance could not be established but it is evident that there is positive correlation between IL - 6 level and CIMT level in normal population.

3. Discussion

We aimed to determine correlation of inflammatory marker & vitamin D level with carotid intima media thickening in prediabetics in a cross sectional study of a sample size of 200 patients. In this study AGE, SEX, SMOKING, HYPERTENSION was equally matched in cases and controls to decrease bias of these risk factors influencing result of the study.

Both fasting and postprandial blood sugar was elevated in cases when compared with controls. The normal intimal - medial thickness of common carotid artery as evaluated by B mode ultrasound imaging was < 0.88 mm approximately. Out of 100 cases 78 had vitamin D level < 30 (61.5 %) and 22 patients had vitamin D level > 30 (38.5 %) whereas out of 100 control 45 had vitamin D level < 30 and 55 patients had vitamin D level >30 hence proving low vitamin D level were more likely to be in prediabetic. Similar results were seen in Dutta's study.

Out of 100 cases 34 patients had CRP between 0 - 6 (45.5 %) and 66 patients had CRP >6 (54.5 %) whereas out of 100 control 57 had CRP between 0 - 6 and 43 had CRP >6. This proves the positive association between high CRP levels and prediabetics.

Out of 100 cases 32 patients had ESR between 0 - 20 (52%) and 68 patients had ESR > 20 (48 %) whereas out of 100 control 72 had ESR between 0 - 20 and 28 had ESR >20, hence proving positive relationship between high ESR and prediabetes and similar results were seen in following study. Out of 100 cases 32 patients had IL - 6 between 0 - 80 (68 %) and 68 patients had IL - 6 > 80 whereas out of 100 control 98 patient had IL - 6 between 0 - 80 and 2 patients had IL - 6 >80 proving a positive relationship between IL - 6 and prediabetics with similar results in following studies.

Out of 100 cases 22 patients had CIMT levels < 0.88 and 78 patients > 0.88 while out of 100 control 92 patients had CIMT levels < 0.88 and 8 patients had > 0.88, proving a positive relationship between raised CIMT levels and prediabetics.

Out of 100 cases, 7 patients had vitamin D < 30 and CIMT < 0.88 while 67 patients had vitamin D < 30 and CIMT > 0.88.15 patients had vitamin D levels > 30 and CIMT < 0.88 while 11 patients had vitamin D > 30 and CIMT > 0.88, while in control patients 34 had vitamin D < 30 and CIMT < 0.88 and 3 patients had vitamin D < 30 and CIMT > 0.88.58 patients had vitamin D levels > 30 and CIMT < 0.88 while only 5 patients showed vitamin D > 30 and CIMT > 0.88 showing a positive correlation between raised CIMT and vitamin D levels.

In group of cases, patients having CIMT < 0.88 the mean N/L ratio was $3.36 \pm 2.406SD$ and patients having CIMT > 0.88 the mean N/L ratio was $1.314 \pm 2.568 SD$, while in the group of controls, patients having CIMT < 0.88 the mean N/L ratio was 5.34 ± 3.522 and patients having CIMT > 0.88 the mean N/L ratio was 8.88 ± 5.919 proving a positive association between CIMT and N/L ratio.

In correlation of CRP by CIMT in the group of cases, 14 patients had CRP between 0 - 6 and CIMT < 0.88, while 20 patients had CRP between 0 - 6 and CIMT > 0.88. 14 patients had CRP > 6 and CIMT < 0.88, 52 patients had CRP between 0 - 6 and CIMT > 0.88. In the group of control, 9 patients had CRP between 0 - 6 and CIMT < 0.88 and only 1 patient had CRP between 0 - 6 and CIMT > 0.88. 73 patients had CRP > 6 and CIMT < 0.88, only 17 patients had CRP > 6 and CIMT > 0.88. This shows the positive association between the two.

In correlation of ESR by CIMT in the group of cases, 18 patients had ESR between 0 - 20 with CIMT < 0.88, 14 patients had ESR between 0 - 20 and CIMT > 0.88, while 10 patients had ESR > 20 with CIMT < 0.88 and 58 patients had ESR > 20 with CIMT > 0.88. In the group of control, 24 patients had ESR between 0 - 20 with CIMT < 0.88, 4 patients had ESR between 0 - 20 and CIMT > 0.88, while 58 patients had ESR > 20 with CIMT < 0.88 and 14 patients had ESR > 20 with CIMT > 0.88. This shows the positive association between the two.

In correlation of IL - 6 by CIMT in the group of cases, only 2 patients had IL - 6 between 0 - 80 with CIMT < 0.88, 12 patients had IL - 6 between 0 - 80 and CIMT > 0.88, while 26 patients had IL - 6 > 80 with CIMT < 0.88 and 60 patients had IL - 6 > 80 with CIMT > 0.88. In the group of control, 40 patients had IL - 6 between 0 - 80 with CIMT < 0.88, 58 patients had IL - 6 between 0 - 80 and CIMT > 0.88, while only 2 patients had IL - 6 > 80 with CIMT < 0.88 and 0 patients had IL - 6 > 80 with CIMT > 0.88. This shows the positive association between the two.

4. Conclusion

- 1) Prevalence of vitamin D deficiency is more in pre diabetics than normal population that is statistically significant.
 - a) The pre diabetics who had increased CIMT level were found to be more deficient for vitamin D which is statistically significant (p Value<0.002).
 - b) In normal population vitamin D was more deficient in cases CIMT level > 0.88 but due to small sample size statistical significance could not be established but it is evident that there is negative correlation between vitamin D level and CIMT level which is tending towards significance.
- 2) CRP level was increased more in pre diabetics than normal population that is statistically significant.
 - a) CRP level was high in pre diabetics who had CIMT level > 0.88 which is statistically significant (p Value<0.001).
 - b) In normal population CRP level was high in cases with CIMT level > 0.88 but due to small sample size statistical significance could not be established but it is evident that there is positive correlation between CRP level and CIMT level which is tending towards significance.
- 3) ESR level was increased more in pre diabetics than normal population that is statistically significant.
 - a) ESR level was high in pre diabetics who had CIMT level > 0.88 which is statistically significant (p Value 0.00005).

- b) ESR level was also high in normal population who had CIMT level > 0.88 which is statistically significant (p Value 0.002).
- 4) IL - 6 level was increased more in pre diabetics than normal population that is statistically significant.
 - a) IL - 6 level was high in pre diabetics who had CIMT level > 0.88 which is statistically significant (p Value - 0.001).
 - b) IL - 6 level was high in normal population who had CIMT level > 0.88 but due to small sample size statistical significance could not be established but it is evident that there is positive correlation between IL - 6 level and CIMT level in normal population which is tending towards significance.
- 5) The pre diabetics had high NLR ratio than normal population.
 - a) High NLR ratio was seen in pre diabetics with CIMT level > 0.88.
 - b) High NLR ratio was also seen in normal population with CIMT level > 0.88.
- 6) CIMT level was more in pre diabetics than normal population that is statistically significant (p Value<0.0001).

Thus, we concluded from our study

- Inflammatory markers (ESR, CRP, IL - 6 and NLR) are increased as the CIMT increases suggesting the role of inflammatory markers in pathogenesis of atherosclerosis in prediabetics.
- Hence, pre diabetics is related to atherosclerosis and may lead to an increased risk of developing CAD in future.
- Therefore, evaluation of inflammatory markers, vitamin D level and measurement of CIMT in pre diabetics can serve as an early marker of atherosclerosis, allowing physicians to plan early interventions to decrease future cardiovascular disease risk.

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