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# Study of Lipid Profile, Atherogenic Indices and Carotid Intima-Media Thickness as Predictors of Cardiovascular Disease in Individuals with Prediabetes

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## ABSTRACT

**Background:** Prediabetes is the forerunner of diabetes mellitus (DM) which is the harbinger of cardiovascular disease because of the covert change in biochemical parameters in the prediabetes state. Atherogenic indices have been utilized for evaluation of the possibility for cardiovascular disease advancement. This study was taken up to estimate the correlation between atherogenic indices, such as cardiac risk ratio (CRR), atherogenic coefficient (AC), and atherogenic index of plasma (AIP) with cardiovascular parameters in the pre-diabetic stage.

**Objectives:** This study was taken up to analyze atherogenic indices (CRR, AC, and AIP) against CIMT (carotid intima-media thickness), which is a surrogate marker in cardiovascular diseases, in prediabetic individuals and find out the correlation between them.

**Methods:** In this cross-sectional study, a total of 120 human individuals were taken among whom 60 were prediabetic individuals and 60 were healthy individuals who served as control. Atherogenic indices were estimated from routine lipid profile parameters and carotid intima-media thickness (CIMT) was determined by ultrasonography in all subjects.

**Results:** There was a significant increase in atherogenic indices, that is, CRR( $P < 0.001$ ), AC( $P < 0.001$ ), and AIP( $P < 0.001$ ), HbA1c( $P < 0.001$ ) and CIMT( $P < 0.001$ ) in prediabetic individuals as compared to controls and the CIMT was significantly positively correlated with atherogenic indices, that is, CRR( $r = 0.514, p < 0.01$ ), AC( $r = 0.514, p < 0.01$ ), and AIP( $r = 0.538, p < 0.01$ ) respectively in the prediabetic group.

**Conclusion:** Atherogenic indices may be utilized along with routine lipid parameters for the better evaluation of subclinical atherosclerosis in prediabetic individuals because these indices are inexpensive, non-invasive and can be determined from routine lipid parameters.

**Key Words:** Atherogenic indices, Atherogenic coefficient (AC), Atherogenic index of plasma (AIP), Carotid intima-media thickness (CIMT), Cardiac Risk Ratio (CRR), Small dense LDL-C (SdLDL-C)

## INTRODUCTION

Diabetes Mellitus is one of the modern epidemics and as per International Diabetes Federation (IDF), the incidence of Type 2 (T2DM) will rise from 366 million in 2011 to 552 million by 2030, affecting one out of ten adults.<sup>1</sup> In Europe, at least 131 billion dollars per year is spent on healthcare due to diabetes.<sup>2</sup> A similar trend exists in South East Asian countries especially India, Nepal etc. The prevalence of DM will become double in people living in the urban area of developing countries in 2030 as compared to the year 2000.<sup>3</sup> Prediabetic stage of diabetes is a longer phase,

which is contemplated to be the harbinger and high-risk state for diabetes.<sup>4</sup>

Prediabetes can be defined as FBS in the range of 100-125 mg/dl.<sup>5,6</sup> IFG and IGT constitute separate pathophysiological and biochemical and combinedly clinically known as "Prediabetes".<sup>7,8</sup> IDF evaluated that the worldwide prevalence of prediabetes was 318 million in the year 2015 and is forecasted to reach 482 million by the year 2040<sup>9</sup> and the same for Nepal was 10.3% in 2017.<sup>10</sup> Prevalence of prediabetes: diabetes in Nepal is 19.5: 9.5%.<sup>11</sup> Many studies have shown pro-atherogenic lipid profile in prediabetes

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leading to cardiovascular disease (CVD).<sup>12-14</sup> Certain atherogenic indices have been formulated which can interlink the metabolic derangement of lipid fractions to clinical findings.<sup>15</sup> The cardiac risk ratio (CRR)<sup>16</sup>, atherogenic coefficient (AC) which is Non-HDL-C: HDL-C correlates better than only LDL-C.<sup>17</sup> Atherogenic index of plasma (AIP) is the logarithmic transformation of the curves that are created by dividing plasma triglyceride (TG) levels by the HDL-C levels and is a better risk predictor for CVD.<sup>18</sup>

Carotid intima-media thickness (CIMT) indicates subclinical atherosclerosis and there is an increase in intima-media thickness (IMT) of both the coronary vascular bed and the peripheral arteries.<sup>19-21</sup> CIMT is determined through measurement of the thickness of the common carotid artery by ultrasound and has been demonstrated as an independent predictor of cardiovascular risk.<sup>22</sup> The study targeted to correlate lipid profile, atherogenic indices: CRR, AC and AIP and CIMT that may be an early marker of atherosclerosis in prediabetic subjects.

## MATERIAL AND METHODS

A cross-sectional observational study was planned in the department of Biochemistry, Nepalgunj Medical College, Kohalpur, Nepal. In this study, a total of 120 human individuals were included among which 60 were prediabetic individuals in 18–55 years old of either gender and 60 were age and gender-matched control from community selected through a predesigned screening questionnaire from January 2019 to December 2019 in Banke district and having at least one of the main standard risk factors for DM like first degree relative with diabetes, Body mass index (BMI)  $\geq 25$  kg/m<sup>2</sup>, women with GDM, PCOS, sedentary lifestyle and other clinical conditions associated with insulin resistance like severe obesity, acanthosis nigricans, etc.

Ethical clearance was obtained from the Institutional Ethics Committee and written and verbal informed consent was obtained from all participants. Based on American Diabetes Association (ADA), the study subjects were diagnosed as prediabetic when fasting plasma glucose level was between 100–125 mg/dL (IFG), and two-hour plasma glucose (after giving 75 g of glucose) level was between 140–199 mg/dL (impaired glucose tolerance, IGT).

Participants having cardiovascular disease, renal disease, T2DM, hepatic disease, acute or chronic inflammatory disease, prolonged illness, pulmonary tuberculosis, gout and arthritis, patients taking medicines that alter glucose and lipid metabolism and plasma TG  $\geq 400$  mg/dl were excluded from the study.

SBP, DBP, Body mass index (BMI), Waist circumference (WC), Hip circumference (HC) and Waist-to-hip ratio

(WHR) were measured by standard methods. The CIMT was calculated by using a high-resolution B mode ultrasonography system with an electrical linear transducer mid-frequency of 7.5 MHz. 7 ml of venous blood samples were taken from all subjects after overnight fasting of 12 hours and 3 days of the fat-free diet, and biochemical parameters were analysed by a fully automated analyzer by standard methods.

Cardiac Risk Ratio was calculated as (CRR) = TC/HDL, Atherogenic coefficient was calculated as (AC) = non-HDL/HDL and atherogenic index of plasma was (AIP) =  $\log$  TG/HDL, where the concentration of TG and HDL are in mmol/L. The entire data were expressed as mean  $\pm$  standard deviation. The data were analyzed by using Statistical Package for Social Science version 16 (SPSS 16). The normal distribution of data was checked by using *Kolmogorov-Smirnov* (K-S) test and intergroup comparisons were analyzed by Student's T-test while the *Mann-Whitney U* test was used for the intergroup comparisons of skewed data. The categorical data were analyzed by using the Chi-square test. The correlation was studied by Pearson's correlation.

## RESULTS

The socio-demographic and biochemical characteristics of the studied individuals are depicted in **Table 1**. There was no statistically significant difference in age and gender between prediabetic and control groups, pointing that data were age and gender-matched. Participants of prediabetes had a statistically significant increase in the mean value of BMI ( $p < 0.001$ ), WC, HC, and WHR ( $p < 0.001$ ) as compared to control participants which demonstrated that prediabetic participants had high central obesity (based on WHR) and general obesity (based on BMI) (**Table 1**). In prediabetic individuals, both systolic blood pressure ( $p < 0.001$ ) and diastolic blood pressure ( $p < 0.001$ ) were significantly raised as compared to controls. There was a statistically significant increase in the lipid profile parameters: total cholesterol ( $p < 0.001$ ), triglyceride ( $p < 0.001$ ), LDL-C ( $p < 0.001$ ), and VLDL-C ( $p < 0.001$ ) in prediabetic individuals as compared to controls whereas prediabetic individuals had significantly lowered HDL values compared to control ( $p < 0.001$ ). In prediabetic individuals, There was a statistically significant rise in HbA1c ( $p < 0.001$ ), CIMT ( $p < 0.001$ ) and atherogenic indices, i.e. CRR ( $p < 0.001$ ), AC ( $p < 0.001$ ), and AIP ( $p < 0.001$ ), as compared with controls (**Table 1**).

In **Table 2**, all the cardiovascular risk factors, i.e. Body mass index (BMI), Waist-to-hip ratio (WHR), systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting plasma glucose (FPG), two-hour post glucose (2 h-PG), Glycated haemoglobin (HbA1c), Total cholesterol (TC), Triglyceride (TG), low-density lipoprotein (LDL-C), and very-low-density lipoprotein (VLDL-C) were found significantly and

positively correlated with Cardiac risk ratio(CRR) atherogenic coefficient (AC), atherogenic index of plasma (AIP) and Carotid intima-media thickness(CIMT) respectively in prediabetics. HDL-C was significantly negatively correlated with CRR ( $r=-0.801$ ,  $p<0.01$ ), AC ( $r=-0.801$ ,  $p<0.01$ ), AIP ( $r=-0.701$ ,  $p<0.01$ ) and CIMT ( $r=-0.342$ ,  $p<0.01$ ) in prediabetic individuals. Additionally, age was found to be statistically significant and positively correlated with AIP ( $r=0.369$ ,  $p<0.01$ ), CRR ( $r=0.399$ ,  $p<0.01$ ), AC ( $r=0.399$ ,  $p<0.01$ ), and CIMT ( $r=0.392$ ,  $p<0.01$ ) in prediabetic subjects, pointing that as the age advances, the risk of cardiovascular disease development increases.

In **Table 3**, lipid profile parameters TC, TG and VLDL were significantly and positively correlated with CRR, AC and AIP whereas HDL was significantly and negatively correlated with CRR ( $r=-0.696$ ,  $p<0.01$ ), AC ( $r=-0.696$ ,  $p<0.01$ ) and AIP ( $r=-0.531$ ,  $p<0.01$ ) in control. But LDL-C was significantly and positively correlated with CRR ( $r=0.745$ ,  $p<0.01$ ) and AC ( $r=0.745$ ,  $p<0.01$ ) whereas age was significantly and positively correlated with CIMT in control individuals. In **Table 4**, atherogenic indices CRR ( $r=0.511$ ,  $p<0.01$ ), AC ( $r=0.487$ ,  $p<0.01$ ) and AIP ( $r=0.544$ ,  $p<0.01$ ) were significantly and positively correlated with CIMT in prediabetic subjects, whereas in control subjects, the correlation was not significant statistically (**Figures 1, 2 & 3**).

## DISCUSSION

Prediabetes state has been considered as a risk factor for diabetes mellitus and cardiovascular diseases (CVD).<sup>23</sup> In this study, the mean fasting plasma glucose, mean 2-h post glucose, and mean glycated haemoglobin (HbA1c) levels have been statistically significantly increased from healthy to prediabetes which corroborates with the previous studies.<sup>24-26</sup>

Dyslipidaemia takes part in the pathophysiology for the development of atherosclerosis and is associated with increased risk for the development of CVD.<sup>27</sup> LDL-C being pro-atherogenic and HDL-C being anti-atherogenic.<sup>28,29</sup> We got statistically significant raised levels of TC, TG, LDL-C, and VLDL-C in prediabetic individuals as compared to controls, whereas HDL-C was significantly decreased which is consistent with previous studies (Table 1).<sup>13,14,27,30</sup> Insulin resistance may lead to inhibition of suppression of lipolysis in adipose tissue that makes high free fatty acid influx in the liver and increases the secretion of hepatic VLDL-C which leads to raised TG levels and decreases the levels of HDL-C.<sup>31,32</sup> It is established that a rise in TG levels raises the level of small dense LDL (sdLDL-C) particles that ultimately lead to increased risk for the advancement of cardiovascular disease.<sup>33</sup> Small dense LDL particles are strongly atherogenic as they promote atherosclerosis by increasing lipid peroxidation.<sup>21</sup>

Hence, the HDL-C is called an antiatherogenic lipoprotein and also harbours paraoxonase anti-oxidant enzymes that have a protective role on atherosclerotic heart disease and low HDL-C is associated with increased risk for CVD and carotid intima thickness.<sup>34-36</sup> In our study, the CRR and AC are statistically significantly increased in prediabetic individuals which are in line with previous study (Table 1).<sup>26</sup> Despite, standardized analysis of Apolipoprotein B is not always accessible in routine clinical practices and hence non-HDL-C is a better alternative.<sup>37</sup> The ratio of non-HDL (atherogenic) and HDL-C (antiatherogenic) determines the increased risk for cardiovascular disease.<sup>38</sup> Recently, the Atherogenic index of plasma (AIP) calculated as  $(\log TG/HDL)$  is considered as an additional indicator and in fact, a better predictor for myocardial infarction and atherosclerotic heart diseases.<sup>39,40</sup> The AIP is negatively correlated with LDL particle size and is positively correlated with the fractional esterification rate of HDL (FERHDL) and also precisely reflects the existence of atherogenic sdLDL-C and HDL-C and is a sensitive predictor of coronary atherosclerosis and cardiovascular risk.<sup>41</sup> It has been proposed that AIP values of  $-0.3$  to  $0.1$  are correlated with low,  $0.1$  to  $0.24$  with medium, and above  $0.24$  with high cardiovascular risk (Table 2).<sup>42</sup>

In this study, AIP values have been found significantly increased in prediabetic individuals as compared to controls, which is consistent with the previous studies<sup>26,43,44</sup> and we got an AIP value of  $0.28 \pm 0.04$  suggesting prediabetics at greater risk (Table 1). Both increases in Intima-media thickness and observation of plaque formation are signs of early-stage atherosclerosis and hence CIMT has been measured as an easy, non-invasive, sensitive, reliable and cheaper marker.<sup>45-47</sup> In this study, there was a significant increase in CIMT values of prediabetic individuals as compared to control individuals which corroborated with previous studies.<sup>26,48</sup>

The increase in thickness of CIMT does not promptly give insight to cardiovascular events but consider the grade of atherosclerosis somewhere in the arterial system.<sup>51</sup> In our study, CIMT significantly and positively correlated with atherogenic indices in prediabetic individuals but not in control which was in line with previous study<sup>26</sup> (**Tables 2-4 and Figures 1-3**) and is similar to other studies.<sup>52,53</sup> Hence it was determined that atherogenic indices can be utilized for the evaluation of the risk of subclinical atherosclerosis in prediabetic individuals. The limitation of this study was the cross-sectional nature of the data that limits the inferences about causal relationships and the sample size.

## CONCLUSION

Our study concluded that the subtle biochemical alteration of atherosclerosis starts even before the onset of diabetes, in the prediabetes state. Hence, if diagnosed at the pre-diabetic

stage preventive measures can be taken for halting the progression to full-blown DM or any of the cardiovascular complications. The atherogenic indices may be utilized along with routine lipid parameters for the better evaluation of sub-clinical atherosclerosis they being inexpensive, non-invasive and being easily determined from routine lipid parameters.

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**Conflict of interest:** None

**Author contribution:** Shrewastwa MK - Study planning, execution, statistical analyses and article writing; Acharya V- Article writing, review and overall supervision; Ray S- Article review

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**Table 1: Socio-demographic and Biochemical characteristics of the control and prediabetic subjects.**

Variables	Control subjects (n=60) (Mean±SD)	Prediabetic subjects (n=60) (Mean±SD)
Age(Years)	38.91±8.01	39.73±8.21 <sup>NS</sup>
Sex(M/F)	39/21	41/19 <sup>NS</sup>
BMI(Kg/m <sup>2</sup> )	23.38 ± 1.01	28.98 ± 1.72 <sup>**</sup>
WC(cm)	81.60±2.92	91.12 ± 4.01 <sup>**</sup>
HC (cm)	95.44± 2.40	96.01 ± 2.59 <sup>*</sup>
WHR	0.85 ± 0.05	0.95± 0.04 <sup>**</sup>
SBP(mmHg)	117.28 ± 2.70	128.00 ± 5.06 <sup>**</sup>
DBP(mmHg)	77.68 ± 3.31	82.07 ± 3.58 <sup>**</sup>
FPG(mg/dL)	91.07 ± 3.73	117.01± 3.52 <sup>**</sup>
2-h PG(mg/dl)	124.96± 7.05	151.44± 5.01 <sup>**</sup>
HbA1c (%)	4.8 ± 0.55	5.9 ± .53 <sup>**</sup>
TG (mg/dl)	121.7 ± 20.05	149.28 ± 19.01 <sup>**</sup>

TC (mg/dl)	181.91± 15.29	195.39 ± 19.80 <sup>**</sup>
HDL-C (mg/dl)	44.96± 4.40	33.77± 3.06 <sup>**</sup>
LDL-C (mg/dl)	115.30±13.79	130.31± 17.98 <sup>**</sup>
VLDL-C (mg/dl)	24.34± 4.01	29.85± 3.92 <sup>**</sup>
CIMT(mm)	0.56±0.02	0.68±0.03 <sup>**</sup>
CRR	3.96 ± 0.20	5.79 ± 0.34 <sup>**</sup>
AC	2.96 ± 0.20	4.78± 0.34 <sup>**</sup>
AIP	0.13 ± .11	0.28 ± 0.04 <sup>**</sup>

BMI: Body mass index; WC: Waist circumference; HC: Hip circumference; WHR: Waist-to-hip ratio; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FPG: Fasting plasma glucose; 2-h PG: 2-h post glucose; HbA1c: Glycated haemoglobin; TC: Total cholesterol; TG: Triglyceride; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; VLDL: Very low-density lipoprotein; CIMT: Carotid intima-media thickness; CRR: Cardiac risk ratio; AC: Atherogenic coefficient; AIP: Atherogenic index of plasma; NS: Not significant; \*Significant at p < 0.05; \*\* Significant at p < 0.001.

**Table 2: Correlation of CRR, AIP, AC, and CIMT with cardiovascular risk factors in prediabetic subjects.**

Variables	CRR (r)	AC(r)	AIP(r)	CIMT(r)
Age (Years)	0.399**	0.399**	0.369**	0.392**
BMI (Kg/m <sup>2</sup> )	0.403**	0.403**	0.375**	0.332**
WHR	0.243**	0.243**	0.227**	0.231**
SBP (mmHg)	0.401**	0.401**	0.399**	0.420**
DBP(mmHg)	0.403**	0.403**	0.346**	0.267**
FPG (mg/dl)	0.598**	0.598**	0.587**	0.545**
2-h PG(mg/dl)	0.567**	0.567**	0.538**	0.541**
HbA1c (%)	0.610**	0.613**	0.601**	0.599**
TG (mg/dl)	0.318**	0.318**	0.799**	0.397**
TC (mg/dl)	0.798**	0.798**	0.312**	0.384**
HDL-C(mg/dl)	-0.801**	-0.801**	-0.701**	-0.342**
LDL-C (mg/dl)	0.871**	0.871**	0.277**	0.362**
VLDL-C (mg/dl)	0.401**	0.401**	0.838**	0.456**

BMI: Body mass index; WHR: Waist-to-hip ratio; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FPG: Fasting plasma glucose; 2-h PG: 2-h post glucose; HbA1c: Glycated haemoglobin; TC: Total cholesterol; TG: Triglyceride; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; VLDL: Very low-density lipoprotein; CRR: Cardiac risk ratio; AC: Atherogenic coefficient; AIP: Atherogenic index of plasma; CIMT: Carotid intima-media thickness; \*\* Significant at p < 0.01 (2-tailed).

**Table 3: Correlation of CRR, AIP, AC, and CIMT with cardiovascular risk factors in control subjects**

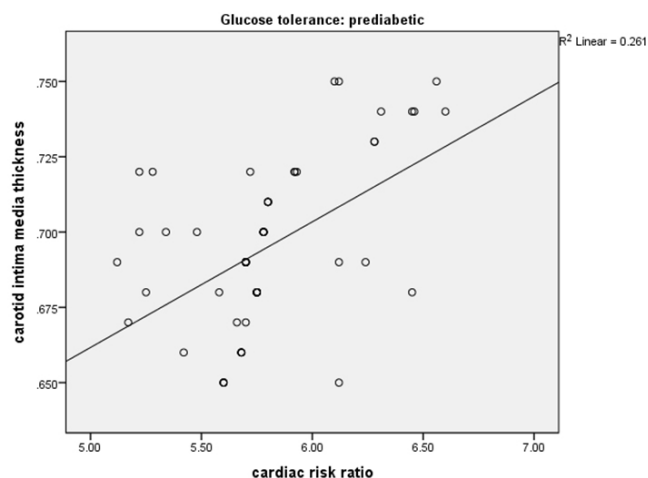
Variables	CRR (r)	AC(r)	AIP(r)	CIMT(r)
Age (Years)	0.076NS	0.075NS	0.004NS	0.343**
BMI (Kg/m <sup>2</sup> )	0.096NS	0.096NS	0.126 NS	-0.002NS
WHR	0.009NS	0.009NS	0.060 NS	0.004NS
SBP (mmHg)	0.061NS	0.062NS	0.110NS	-0.010NS
DBP(mmHg)	0.131NS	0.131NS	-0.013NS	0.062NS
FPG (mg/dl)	0.098NS	0.098NS	0.086NS	0.091NS
2-h PG(mg/dl)	0.062NS	0.062NS	0.092NS	0.051NS
HbA1c (%)	0.094NS	0.094NS	0.100NS	0.045NS
TG (mg/dl)	0.261**	0.261**	0.836**	0.062NS
TC (mg/dl)	0.698**	0.698**	0.165*	0.060NS
HDL-C(mg/dl)	-0.696**	-0.696**	-0.531**	-0.071NS
LDL-C (mg/dl)	0.745**	0.745**	0.031NS	0.061NS
VLDL-C (mg/dl)	0.261**	0.261**	0.899**	0.063NS

BMI: Body mass index; WHR: Waist-to-hip ratio; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FPG: Fasting plasma glucose; 2-h PG: 2-h post glucose; HbA1c: Glycated haemoglobin; TC: Total cholesterol; TG: Triglyceride; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; VLDL: Very low-density lipoprotein; CRR: Cardiac risk ratio; AC: Atherogenic coefficient; AIP: Atherogenic index of plasma; CIMT: Carotid intima-media thickness; NS: not significant ; \* significance at < 0.05; \*\* Significant at p < 0.01 (2-tailed).

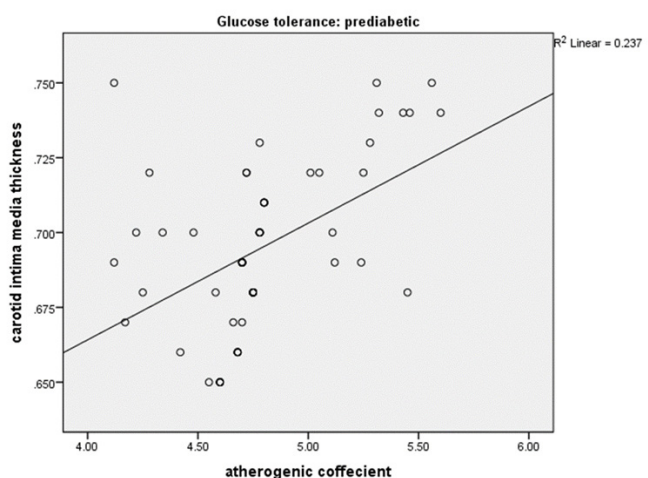
**Table 4: Correlation of atherogenic indices with CIMT in prediabetic and control subjects.**

Variables	CIMT	
	Prediabetic (r)	Control(r)
CRR	0.511**	0.007 <sup>NS</sup>
AC	0.487**	0.10 <sup>NS</sup>
AIP	0.544**	0.005 <sup>NS</sup>

CRR: Cardiac risk ratio; AC: Atherogenic coefficient; AIP: Atherogenic index of plasma; CIMT: Carotid intima-media thickness; NS: Not significant; \*\* Significant at p < 0.01 (2-tailed).



**Figure 1: Correlation between carotid intima media thickness and cardiac risk ratio.**



**Figure 2: Correlation between carotid intima media thickness and atherogenic coefficient.**

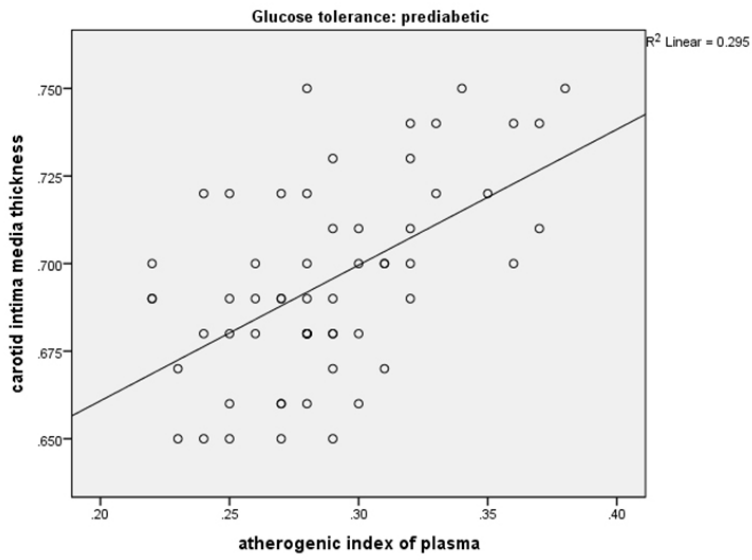


Figure 3: Correlation between carotid intima media thickness and atherogenic coefficient.