



Research Article

Calcified Coronary Lesions in Diabetes – Culmination of Dyslipidaemia and Inflammation

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Abstract

Objectives: Cardiovascular diseases are the major cause of mortality amongst diabetic patients.

This study was conducted to compare anthropometric, haematological and lipid variables in diabetic and non-diabetic Indians. The presence of coronary calcifications on the angiogram was further associated with above variables.

Methods: Prospective study in 1000-bedded hospital in North-India, comprising 105 (30 diabetic, 75 non-diabetic) patients undergoing coronary angiography. Hypertension, smoking, alcohol intake, statin >6 months, previous MI were excluded. Lipid profile, HbA1c, BMI, waist-hip ratio, complete blood count, mean platelet volume (MPV), was measured. Continuous variables were correlated using correlation coefficients, and compared between diabetes and coronary-calcification groups, using a t-test. Chi-square-test used for associating diabetes with coronary calcifications.

Results: Triglyceride-HDLc-ratio, Neutrophil-Lymphocyte-Ratio, WHR and MPV most significantly differed between diabetics and non-diabetics ($p < 0.01$) and correlated well with HbA1c ($p < 0.001$). Total cholesterol and LDLc were not significant. Patients with coronary calcifications had higher neutrophil-lymphocyte-ratio ($p < 0.01$), as compared to TLC ($p < 0.05$). Diabetics were more likely to have coronary calcifications ($p < 0.05$, OR 3.25 95%CI 1.184-8.920).

Conclusion: Central obesity and dyslipidaemia contribute to chronic inflammation in diabetes with cardiac complications. Triglyceride-HDLc-ratio, Neutrophil-Lymphocyte-Ratio, and MPV are simple, inexpensive markers for dyslipidaemia and inflammation, assuming significance in low-resource settings.

Keywords: Angiography, diabetes mellitus, dyslipidemias, vascular calcification

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Diabetes mellitus is one of the fastest-growing health challenges of the 21st century. The global burden of diabetes is growing with approximately 463 million adults between 20-79 years of age living with diabetes, and 11.3% (4.2 million) of total deaths are attributable to the diabetes worldwide.^[1] The continued increase in prevalence of diabetes is in part because of the increase in Type 2 diabetes, caused by continued urbanisation, sedentary lifestyles, high-calorie food intake and physical inactivity. Insulin resistance (IR), obesity, dyslipidaemia, and metabolic syndrome constitute the components of a complex web of causation. This overlapping array of the risk factors contrib-

utes to these non-communicable diseases, and their future complications.

Cardiovascular disease (CVD) has become the leading cause of mortality in India and the world, and in diabetes is the commonest cause of death.^[2] Approximately 17.9 million deaths in 2016 were attributable to CVDs, which constitutes 31% of global deaths.^[3] Parallely, an obesity epidemic driven by calorie-dense foods and sedentary lifestyles, contributing to diabetes prevalence, is recognized both in urban and rural India.^[4]

Complications of diabetes are numerous, ranging from ischaemic heart disease, stroke and gangrene to retinopathy,

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neuropathy and nephropathy. Undiagnosed and uncontrolled diabetes is associated with a significant deterioration in quality of life, especially in rural India where a wide gap exists between health care facilities, management and implementation. Early identification of risk factors and intervention is paramount for the prevention of cardiac complications in diabetes, to reduce the morbidity and mortality of the disease. This study aimed to compare diabetic and non-diabetic patients without other comorbidities, undergoing diagnostic coronary angiography in Northern India. Significant differences in anthropometric, inflammatory and lipid variables are identified, to explore their utility as markers for disease prognosis and coronary artery calcifications.

Methods

This was a prospective study consisting of 105 patients (30 diabetic and 75 non-diabetic) who were referred for coronary angiography in a 1000 bedded tertiary care hospital in Northern India during the period May 2018 to Feb 2019. The study was conducted after obtaining approval from the Institutional Ethics Committee and written informed consent from all participants.

All patients >18 years of age undergoing diagnostic coronary angiography for the first time were included. Patients with a history of active infection, hypertension, smoking, alcohol intake, and of taking lipid-lowering medications for > 6 months were excluded. Patients with a history of previous coronary angiography or cardiac insult were also excluded.

Sample Collection and Analysis

Demographic information and clinical history were collected from all participants prior to angiography. Anthropometric measurements like height, weight, waist circumference and hip circumference were obtained using standard procedures. Body mass index (BMI) and waist/hip ratio (WHR) was also calculated for each subject. Coronary angiography was performed by percutaneous radial or femoral puncture, using the standard Judkin technique. Presence of plaques in the left anterior descending artery, left circumflex artery and right coronary arteries were noted for each patient. Presence of any coronary calcifications as seen on the angiogram were also recorded.

Lipid parameters such as total cholesterol (Tc), triglyceride (TG), and high-density lipoprotein cholesterol (HDLc) were estimated on a fully automated biochemistry analyser, EM360-Transasia. Low-density lipoprotein cholesterol (LDLc) and very low-density lipoprotein cholesterol levels (VLDLc) were calculated as per Friedwald's equation. TG/HDLc ratio was also calculated. HbA_{1c} levels were estimated on a fully automated D-10 analyser. A complete blood

count was performed on an automated haematology cell counter with 3-part differential, Sysmex KX-21 (Sysmex Corporation, Kobe, Japan). Total and differential leukocyte count (TLC and DLC), and absolute neutrophil and lymphocyte counts (ANC and ALC) were calculated. Platelet count and mean platelet volume (MPV) were estimated from the same given sample. Neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) were recalculated.

Statistical Analysis

Statistical Analysis was performed using SPSS version 21.0 for Windows (Armonk, NY: IBM Corp). Categorical variables are expressed as a percentage and continuous variables as mean±SD. Normality of data was assessed using the Shapiro-Wilk test. At-test or Mann-Whitney U test were used as appropriate to compare groups. A Pearson or Spearman correlation coefficient was calculated as appropriate to determine the correlation between continuous variables. Chi-square test was applied to test the relationship between categorical variables, and odds ratio was estimated.

Results

This study consisted of 30 diabetic and 75 non-diabetic patients, aged between 42 to 84 years with a mean age of 61.76±9.05 years. Males comprised 60% of diabetics (18/30), and 76% of non-diabetics (57/75). The mean age amongst diabetics and non-diabetics was 61.23±9.52 and 61.97±8.91 respectively.

A t-test was used to compare means between diabetics and non-diabetics. The non-parametric variant (Mann Whitney U test) was used when data was non-normal. Diabetics on average had significantly higher WHR, TG, VLDLc, TG/HDL, and significantly lower HDLc levels, compared to non-diabetics. No significant differences were observed between diabetics and non-diabetics for LDLc and Tc levels. The results are summarized in (Table 1).

Table 1. BMI, WHR and lipid variables in diabetics vs non-diabetics

	Mean±SD		Significance
	Non-Diabetics	Diabetics	
BMI (kg/m ²)	24.72±3.51	25.27±2.59	t=-0.76, p=0.446
WHR	0.99±0.072	1.03±0.073	t=-2.67, p=0.009
HbA _{1c} (%)	5.41±0.782	7.06±2.02	U=507.5, p<0.001
TG (mg/ dL)	127.18±43.76	145.46±38.30	U=820.5, p=0.031
LDLc (mg/dL)	80.21±32.50	78.84±37.60	t=0.187, p=0.852
VLDLc (mg/dL)	25.43±8.75	29.09±7.66	U=820.5, p=0.031
HDLc (mg/dL)	47.26±12.59	41.86±8.49	t=2.54, p=0.013
Tc (mg/dL)	152.91±35.33	150.06±42.02	U=1016.0, p=0.439
TG/HDLc Ratio	2.92±1.42	3.62±1.37	U=742.5, p=0.007

A correlation coefficient was computed to determine the relationship of BMI and WHR, with HbA1c and various lipid parameters. WHR showed a positive correlation with HbA1c, VLDLc, TG, and TG/HDLc, and a negative correlation with HDLc. There was no significant correlation between WHR and LDLc or Tc. BMI showed significant positive correlation with TG/HDLc; however, no correlation was observed for HbA1c, TG, LDLc, Tc, VLDLc or HDLc. The results are summarized in (Table 2).

HbA1c levels showed a positive correlation with MPV, TLC, ANC, NLR, PLR and TG/HDLc, and a significant negative correlation with ALC. There was no statistically significant correlation between HbA1c and platelet count. The results are summarized in (Table 3).

Diabetics also had higher TLC, MPV, ANC, NLR and PLR, and lower ALC compared to non-diabetics. No significant difference in platelet count existed between diabetics and non-diabetics. The results are summarized in (Table 4).

The left anterior descending artery was the most commonly involved artery amongst both diabetics and non-diabetics. Involvement of all three major vessels (triple vessel disease) was present in 32.4% (34/105) of patients. Frequencies of coronary lesions amongst diabetics and non-diabetics are summarized in (Table 5).

Table 2. Correlation coefficients of BMI and WHR with HbA1c and lipid variables

	Correlation Coefficient	
	Body Mass Index	Waist Hip Ratio
HbA _{1c}	r=0.021, p=0.833	r=0.471, p<0.001
TG	r=0.160, p= 0.103	r=0.346, p<0.001
LDLc	r=-0.074, p=0.454	r=0.018, p=0.858
VLDLc	r=0.160, p=0.103	r=0.346, p<0.001
HDLc	r=-0.107, p=0.276	r=-0.265, p<0.01
Total Cholesterol	r=-0.041, p=0.676	r=-0.011, p=0.914
TG/HDLc Ratio	r=0.203, p=0.038	r=0.408, p<0.001

Table 3. Correlation coefficients of HbA1c for leukocyte and platelet parameters, and TG/HDLc ratio

	Correlation Coefficient
	HbA1c
MPV	r=0.333, p=0.001
Platelet Count	r=0.072, p=0.468
TLC	r=0.357, p<0.001
ANC	r=0.317, p=0.001
ALC	r=-0.253, p=0.009
NLR	r=0.391, p<0.001
PLR	r=0.232, p=0.017
TG/HDLc Ratio	r=0.500, p<0.001

Table 4. Leukocyte and platelet parameters in diabetics vs non-diabetics

	Mean±SD		Significance
	Non - Diabetics	Diabetics	
TLC (x10 ⁹ /L)	7.42±1.67	9.28±2.74	U=681.5, p=0.002
Platelet Count (x10 ⁹ /L)	205.96±61.22	208.69±74.26	t=-0.194, p=0.846
MPV (fL)	9.67±1.62	12.06±2.52	U=519.0, p<0.001
ANC (x10 ⁹ /L)	4.29±1.23	5.9±2.3	U=659.5, p=0.001
ALC (x10 ⁹ /L)	2.20±0.72	1.80±0.51	t=3.10, p=0.003
NLR	2.20±1.13	3.67±2.17	U=531.5, p<0.001
PLR	103.12±53.81	127.37±61.08	U=835.0, p=0.040

Table 5. Frequency of coronary lesions in diabetics vs non-diabetics

	Non - Diabetics (n=75)	Diabetics (n=30)
Left Anterior Descending Artery	50 (66.7)	21 (70.0)
Left Circumflex Artery	31 (41.3)	19 (63.3)
Right Coronary Artery	36 (48)	18 (60)
Triple Vessel Disease	20 (26.7)	14 (46.7)

Patients with coronary calcifications (n=20) on average had a higher level of NLR, ANC and TLC compared to patients without coronary calcifications (n=85). No significant differences in means were observed between these groups for TG/HDLc, HbA1c, ALC, MPV or PLR. The results are summarized in (Table 6).

Amongst diabetics, 10 out of 30 subjects (33.3%) showed calcifications on coronary angiogram, and amongst non-diabetics, 10 out of 75 (13.3%) showed calcifications. A chi-square test showed a significant association between diabetes and the presence of calcifications on coronary angiogram ($\chi^2=5.55$, p=0.018). Calcifications occurred more frequently in diabetics than non-diabetics, (Odds Ratio [OR], 3.25; 95% confidence interval [CI], 1.184–8.920).

Table 6. TG/HDLc, HbA1c, leukocyte and platelet parameters in patients with vs without coronary calcifications

	Mean±SD		Significance
	Calcification Absent	Calcification Present	
TG/HDLc Ratio	3.03±1.33	3.50±1.79	U=725, p=0.308
HbA _{1c} (%)	5.75±1.24	6.44±2.1	U=709, p=0.250
NLR	2.50±1.63	3.15±1.59	U=544.0, p=0.013
ANC (x10 ⁹ /L)	4.53±1.60	5.73±2.16	U=536.5, p=0.011
ALC (x10 ⁹ /L)	2.10±0.70	2.00±0.64	U=744, p=0.387
TLC (x10 ⁹ /L)	7.72±2.05	8.94±2.53	U=606.5, p=0.047
MPV	10.17±2.00	11.10±2.81	U=781, p=0.281
PLR	108.88±59.41	114.99±44.70	U=694, p=0.203

Discussion

This study compares lipid, anthropometric and haematological parameters amongst Indian diabetics and non-diabetics not having any other co-morbid conditions, referred for angiography. CAD, being the major cause of morbidity and mortality in diabetes, this study was conducted to explore the relationship of glycaemic control (HbA1C) with inflammation and dyslipidaemia. Furthermore, angiographic profiling of the study population enabled the correlation of diabetes with inflammatory changes observed as coronary calcifications. Platelet indices, leukocyte ratios and lipid profiling are effective measures of prognosis in diabetes and the cardiovascular sequelae thereafter. These easily accessible and inexpensive blood investigations are used here to compare diabetics and non-diabetics.

In this study, central obesity, measured as the WHR, was significantly correlated with HbA1c, TG, VLDLc and HDLc. WHR also showed a stronger correlation with TG/HDLc rather than the individual parameters TG or HDLc. BMI showed no correlation with these parameters, except for TG/HDLc. A significant difference was observed between diabetics and non-diabetics for WHR, but not BMI (Tables 1, 2). Studies suggest that central adiposity is a better predictor of dyslipidaemia, CVDs and IR than BMI alone.^[5,6] With significant variations across ethnicities, the classification of persons as non-obese or obese as per BMI alone may hence be inadequate.^[7] Some studies also show that WHR, more so than BMI, is a significant risk factor for CAD in some populations.^[8] Amongst Asians, many individuals who do not qualify as obese as per BMI guidelines would have considerably greater cardiovascular risk if WHR was used for stratification.^[9]

It is becoming increasingly apparent that dietary cholesterol has no association with diabetes or cardiovascular disease.^[10,11] While some studies have implicated low HDLc and rising LDLc levels in the pathogenesis of heart disease, other studies show no association between LDLc or even Tc levels and heart disease.^[12,13] TG has been established as an independent risk factor for coronary heart disease.^[14] TG/HDLc ratio has been suggested to be a novel marker for insulin resistance besides atherogenicity and extensive coronary disease.^[15,16] TG/HDLc was correlated with both WHR and BMI in this study. Likewise, a significant difference in mean HDLc, TG, VLDLc and TG/HDLc was observed between diabetics and non-diabetics, with TG/HDLc being the most significant (Tables 1, 2). TG/HDLc is an easy-to-calculate index that is increasingly being recognized as an effective surrogate marker for glycaemic control and cardiovascular disease, assuming importance where HOMA-IR or coronary angiography are not feasible.^[17,18] Furthermore,

our study found that HbA1c showed the largest correlation with TG/HDLc, indicating the association between poor glycaemic control and dyslipidaemia (Table 3).

The TG/HDLc has been shown to be strongly associated with the presence of small dense LDLc particles.^[19,20] Total LDLc levels show little association with heart disease, as only the small dense LDLc particles are responsible for atherogenicity.^[20,21] The traditional notion of labelling LDLc as bad-cholesterol stands incorrect, though the estimation of LDLc subfractions is difficult to perform in clinical practice.

Inflammation and poor glycaemic control go in hand in the development of cardiovascular complications in diabetes. Chronic low-grade inflammation is implicated in the pathogenesis, and increased levels of plasma inflammatory markers such as CRP, IL-6 and TNF- α have been found in patients with metabolic syndrome and overt diabetes mellitus.^[22,23] Tight glycaemic control is paramount in the prevention of endothelial dysfunction. Our study found a significant correlation between HbA1c levels and TLC, ANC, ALC, NLR and PLR, with NLR the most significant (Table 3). A difference in means was also seen between diabetics and non-diabetics for these parameters (Table 4). NLR is an effective measure of chronic inflammation, responsible for the development of both diabetes, and its various complications.^[24,25,26] In contrast, TLC, ANC and ALC alone are proven to not be good predictors.^[27] The effectivity of NLR as a marker for inflammation makes it suitable for peripheral health centres where other assays remain out of reach.

On angiography, the left anterior descending artery was the most commonly occluded vessel among all study participants, and diabetic subjects in general had an increased frequency of involvement of all three major coronary vessels individually (Table 5). However, these results were largely coincidental and statistically insignificant. In this study, the presence of coronary calcifications was the variable of choice to quantify the inflammatory consequences on the heart. Atherosclerosis is an entity of chronic inflammation, and intimal calcifications occur later in the disease process. Subjects with coronary calcifications had significantly higher NLR, ANC and TLC, with NLR more significant than TLC (Table 6). No significant differences were observed for any lipid variables. Furthermore, patients with calcifications were around three times more likely to be diabetic compared to those without calcifications in our study. Both diabetes and NLR have been used for risk stratification in previous studies, where patients underwent computed tomography coronary artery calcium scoring.^[28] These results are well explained by chronic low – grade inflammation being the common denominator of the diabetic state. Dyslipidaemia contributes to inflammation, which is responsible

for direct insult to the endothelium. Calcifications ultimately produce impaired myocardial perfusion, resulting from reduced vascular compliance, and abnormal vasomotor response in the coronary vasculature.^[29]

Lastly, no significant results were observed for platelet count, but MPV varied significantly between diabetics and non-diabetics and was significantly correlated with HbA1c (Table 3 and 4). Diabetics exhibited increased platelet reactivity, measured by MPV. The underlying physiology is explained by insulin deficiency or insulin resistance which causes activation of platelets.^[30] Hyperglycaemia contributes to glycation of platelet proteins and platelet reactivity, which further contributes to heart disease. While several markers for platelet reactivity exist, MPV is the least expensive and requires the least sample volume and time, and is particularly useful in low-resource settings, like TG/HDLc and NLR described earlier.

Conclusion

This study examined anthropometric, haematological and lipid variables in diabetic and non-diabetic Indians, with or without calcified coronary lesions on angiography. WHR differed more significantly than BMI between diabetics and non-diabetics in this population. Likewise, TG, HDLc were of significance, and these parameters also correlated well with WHR and HbA1c. Tc and LDLc did not play a role despite the traditional notion of bad cholesterol, however TG/HDLc, indicative of small dense LDL particles, showed the most significant correlations with HbA1c and WHR. Diabetics also had higher levels of inflammatory markers, with NLR more significant than TLC, ANC or ALC. Diabetics were more likely to have calcified coronary lesions, and NLR and TLC were higher on average in persons with calcified lesions. Platelet reactivity measured as MPV was significantly higher in diabetics and correlated strongly with glycaemic control. The utility of comprehensive markers like NLR, TG/HDLc ratio and MPV is explored in this study. They are of great significance in low-resource economies where monitoring disease prognosis with unconventional assays is not feasible.

Disclosures

Limitations: This study had a limited sample size. Studies on larger samples are necessitated to study multiple risk factors at once and to formulate reliable cut-offs for target variables. Additionally, ethnic specific variations warrant further investigations on diverse populations, to account for variable contributions of risk factors into disease causation.

Ethics Committee Approval: The study was approved by the Institutional Ethics Committee of Base Hospital Delhi Cantt, New Delhi, India, on 10th May 2018, (IEC No. BHDC/12/2018).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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