

Assessment of atherogenic index of plasma, non-HDL cholesterol and other cardiac indices as risk factors for CVD in type II diabetes**Shikha Rawat¹, Sudeep Kumar^{2*}, Manisha Arora³, Shahid Iqbal⁴, Jyoti Batra⁵, Shivani Sharma⁶, Sumesh Prasad Sah⁷**¹*Assistant Professor, Department of Biochemistry, Mulayam Singh Yadav Medical College Meerut, UP, India*²*Assistant Professor, Department of Biochemistry, Muzaffarnagar Medical College Muzaffarnagar, UP, India*³*Professor, Department of Metabolism and Nutrition, Medical University of the Americas, Nevis*⁴*Associate Professor, Department of Biochemistry, Muzaffarnagar Medical College, Muzaffarnagar, UP, India*⁵*Professor, Department of Biochemistry, Santosh Medical College, Ghaziabad, UP, India*⁶*Professor, Department of Physiology, Medical University of the Americas, Nevis*⁷*Demonstrator, Department of Biochemistry, Muzaffarnagar Medical College, Muzaffarnagar, UP, India*

Received: 14-07-2020 / Revised: 01-09-2020 / Accepted: 06-09-2020

Abstract

Introduction: Diabetic dyslipidemia is regarded as risk factor for development of cardiovascular disease and it is the primary cause of morbidity and mortality in diabetes. LDL- cholesterol is primarily used as the marker of CVD risk while other markers like lipid ratios, AIP and atherogenic coefficient are the better markers for the prediction of CVD. **Objective:** The present study was aimed to evaluate the non-HDL cholesterol, AIP and other cardiac indices as CVD risk in diabetic patients. **Material & Methods:** This cross-sectional study was carried out in the Department of Biochemistry and Department of Medicine Muzaffarnagar Medical College, Muzaffarnagar. Total 240 patients were enrolled for this study, out of which 120 were diabetic and 120 were normal healthy control of both the sexes. Anthropometric parameters like age, weight, height, blood pressure and the biochemical parameters including fasting blood sugar, lipid parameters, cardiac risk ratio, atherogenic index of plasma, atherogenic coefficient and non-HDL cholesterol were measured. For statistical analysis SPSS version 16 was used and for significance, p-value less than 0.05 was considered. **Results:** In this study, the fasting blood glucose, HbA1c, Total cholesterol, triglycerides, LDL-cholesterol were found to be increased significantly and HDL- cholesterol was found to be decreased significantly in Diabetic patients as compared to normal healthy control. The cardiac indices like, Cardiac Risk ratio (CRR), atherogenic Index of plasma (AIP), atherogenic coefficient (AC) and non-HDL cholesterol were also found to be increased significantly in diabetic patients as compared to normal healthy individuals. **Conclusion:** The present study concluded that the lipid ratios are more convenient clinically and they can be useful in assessing the cardiovascular complications in diabetic patients instead of lipid profile alone.

Keywords: Non-HDL Cholesterol, Atherogenic Coefficient, Cardiac Risk Ratio, Dyslipidemia.

This is an Open Access article that uses a fund-ing model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>) and the Budapest Open Access Initiative (<http://www.budapestopenaccessinitiative.org/read>), which permit unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited.

Introduction

Diabetes mellitus (DM) is one of the major global

disorder; characterized by long standing hyperglycemia due to absolute or relative deficiency of insulin secretion or its action.[1] The dyslipidemia presents a major [probably the most important] link between diabetes and cardiovascular disease. Diabetic dyslipidemia has been the main focus of discussions regarding the interaction between glucose and lipid metabolism.[2] The risk of CV mortality in patients

**Correspondence*

Dr. Sudeep Kumar

Assistant Professor, Department of Biochemistry, Muzaffarnagar Medical College, Muzaffarnagar, U.P., India.

E-mail: sudeepty@gmail.com

with type 2 diabetes (T2DM) is 2-4 times that observed in individuals without diabetes.[3] Indian people are genetically predisposed to the development of cardiovascular disease due to dyslipidemia and decreased levels of high density lipoproteins.[4] Many researchers found that the non-high density lipoprotein cholesterol (non-HDL-C) may be more powerful biomarker for prediction of cardiovascular disease as compared to low density lipoprotein-cholesterol alone. [5, 6] This indicates that many diabetic patients fail to reach goals for non-HDL-C. They meet their target LDL cholesterol goal but still develop complications from atherosclerotic vascular disease and suffer from cardiovascular events. Non-HDL cholesterol is identified as the corrective target at that level of TG. Non-HDL cholesterol may be considered as a marker for predicting CVD and it is calculated by subtracting HDL cholesterol from total cholesterol. The calculating non-HDL-C and other lipid ratios could be more effective than all lipoproteins. [6] Lipid ratios have also been found to indicate an atherogenic risk and are said to better predictors of cardiovascular diseases than lipids alone. Instead of lipid parameters, increased lipoprotein ratios have a better statistical association with severity and prevalence of Coronary Artery Disease (CAD) [7]. Many factors account for increased cardiovascular disease risk in diabetes but lipid abnormalities are major contributors. It is well known that people with diabetes have increased cardiovascular risk. Early assessment and control of CV risk factors in patients with T2DM has a positive effect on reducing the risk of CVD and death in patients and improving the prognosis of patients. Now days, researchers have focused on a new lipid index, the atherogenic index of plasma (AIP), which might comprehensively reflect the balance between atherogenic and anti-atherogenic factors. many researchers in their study showed that AIP, a better marker for predicting the risk of CAD.[8-10] A study conducted in Iran, showed a positive association between AIP, waist circumference and body mass index and negative association with physical activity.[8] Ath-erogenic index of plasma (AIP) is calculated as $\log(TG/HDL-C)$ and it has been designated as a predictor of atherosclerosis and surrogate of small low-density lipoprotein particle size.[11, 12]. Hence the present study was aimed to assess the Atherogenic coefficient and Atherogenic index of plasma and other cardiac indices in assessing Cardiovascular risk in Diabetic patients. These all are calculated fractions which may be used in the clinical laboratory for assessing the risk of cardiovascular disease beyond the routinely done lipid profile.

Materials and Methods

This study was carried out in the Department of Biochemistry and Outpatient Department of Medicine Muzaffarnagar Medical College, Muzaffarnagar from February 2019 to August 2019. The cases were selected from those who attended the Medicine Outpatient Department at Muzaffarnagar Medical College and Hospital, Muzaffarnagar. The sample size was calculated by using the prevalence rate of Diabetes Mellitus in Western UP (8.03%),[13] so the sample size of the study was around 113.48. Permission from the ethical committee and informed consent were taken from every subject. All the investigations were done in the Biochemistry Department, Muzaffarnagar Medical College and Hospital, Muzaffarnagar.

Inclusion Criteria

A total of 240 subjects of both sex groups were enrolled for this study. Out of which 120 were Diabetic (As per IDF criteria) and 120 were normal healthy non-diabetic individuals which was serve as controls for this study.

Exclusion Criteria

The subjects with hepatic disease, cardiovascular disease, any chronic or acute inflammatory illness, all types of cancer, pulmonary tuberculosis, addiction to alcohol, who smoke and having prolonged illness were excluded from the study.

Collection of Blood Sample

About 5 ml of blood was drawn after an overnight fast under aseptic precautions from clinically diagnosed type 2 DM patients and controls. Fasting plasma glucose level and lipid parameters were done by enzymatic method by using automated analyzer. Cardiac Risk ratio, Atherogenic Index of Plasma, non-HDL cholesterol and Atherogenic Coefficient were calculated as follows:

1. CRR (Cardiac Risk Ratio) = Total Cholesterol / HDL-Cholesterol
2. AC (Atherogenic Coefficient) = (Total Cholesterol-HDL cholesterol) / HDL-cholesterol
3. AIP = \log Triglyceride / HDL-cholesterol (mmol/l)
4. Non-HDL-cholesterol = Total Cholesterol – HDL-cholesterol

Statistical Analysis

SPSS version-16 was used for Statistical analysis and a $p < 0.05$ was considered as statistically significant. The statistical differences between the groups were determined by student independent sample t-test.

Results

240 patients were enrolled for this study; out of which 120 were diabetic and 120 normal healthy individuals of both the sex. Table 1 represents the demographic parameters in diabetic and normal healthy individuals. The mean values of weight, BMI, systolic and diastolic blood pressure were increased significantly in diabetic patients as compared to controls.

The table 2 represents the biochemical parameters of normal and diabetic patients. The mean value of FBS, HbA1c, TC, TG, LDL-cholesterol, Non HDL-cholesterol, CRR, AC and AIP were found to be increased significantly in diabetic patients as compared to normal healthy individuals.

Table 1: Showing Demographic parameters in diabetic and normal healthy individual

| S.No. | Variables | Diabetics | Healthy Controls | p-Value |
|-------|-------------------------------------|---------------|------------------|---------|
| 1 | Age (years) | 38.72 ± 9.50 | 37.17 ± 10.12 | 0.22 NS |
| 2 | Weight (Kg) | 59.27 ± 4.16 | 76.17 ± 8.19 | <0.001S |
| 3 | Height (Meter) | 1.59 ± 0.033 | 1.67 ± 0.046 | <0.001S |
| 4 | BMI (Kg/Meter ²) | 23.38 ± 1.38 | 27.39 ± 3.21 | <0.001S |
| 5 | Systolic Blood pressure (mm of Hg) | 119.47 ± 7.33 | 129.57 ± 8.56 | <0.001S |
| 6 | Diastolic Blood Pressure (mm of Hg) | 78.58 ± 3.38 | 84.30 ± 4.28 | <0.001S |

Table 2: Showing biochemical parameters and cardiac indices in diabetic and normal healthy individual

| S.No. | Variables | Diabetics | Healthy Controls | p-Value |
|-------|-------------------------------|----------------|------------------|---------|
| 1 | Fasting Blood Glucose (mg/dL) | 177.74 ± 21.35 | 96.66 ± 8.53 | <0.001 |
| 2 | HbA1c | 8.28 ± 1.7 | 5.16 ± 0.62 | <0.001 |
| 3 | Total Cholesterol | 240.08 ± 22.58 | 174.00 ± 16.65 | <0.001 |
| 12 | Triglyceride (mmol/L) | 2.29 ± 0.165 | 1.55 ± 0.11 | <0.001 |
| 13 | HDL-cholesterol (mmol/L) | 1.02 ± 0.11 | 1.14 ± 0.14 | <0.001 |
| 6 | LDL-cholesterol (mg/dL) | 159.86 ± 22.20 | 100.65 ± 24.15 | <0.001 |
| 7 | VLDL-cholesterol | 40.62 ± 2.93 | 27.45 ± 2.00 | <0.001 |
| 8 | Non-HDL-cholesterol (mg/dL) | 200.48 ± 22.83 | 129.77 ± 21.53 | <0.001 |
| 9 | Cardiac Risk Ratio | 5.13 ± 0.86 | 3.03 ± 0.83 | <0.001 |
| 10 | Atherogenic Index of Plasma | 0.71 ± 0.071 | 0.134 ± 0.063 | <0.001 |
| 11 | Atherogenic Coefficient | 6.13 ± 0.86 | 4.03 ± 0.83 | <0.001 |

Discussion

The prevalence of diabetes mellitus increases continuously and become one of the common prevalent diseases. A strong association was found between diabetes and cardiovascular disease, which is the most cause of morbidity and mortality in diabetic patients. Cardiovascular risk factors such as hypertension, obesity, dyslipidemia are common in diabetic patients and enhances the risk for cardiac events. [14] A researcher in their study reported that the incidence of CVD in diabetic patients was three times more and it has become the major risk factor for diabetic associated morbidity and mortality.[15]

In the present study, the AIP is found to be increased in diabetic patients as compared to healthy individual and it was statistically significant. Our results are in accordance with the many researchers. [16-19] AIP is a

simple relationship between TG and HDL cholesterol and can be considered as good predictor of atherosclerosis [20]. The cardiac risk ratio and atherogenic coefficient were found to be increased significantly in diabetic patients as compared to normal healthy individual. Our results are in agreement with many researchers.[21, 22]. Risk factors for more aggregation in patients with T2DM include insulin resistance, central obesity, elevated blood pressure, and elevated triglycerides. It may be due to increased oxidative stress, increased inflammation, or endothelial cell dysfunction in association with low HDL cholesterol. [23] The risk factors associated with increased AIP are closely related to those for CVD and cerebrovascular disease in patients with Diabetes. In the present study we have observed significant increased level of non HDL cholesterol in diabetic patient as compared to normal healthy individual. Many

researchers were obtained same results. [24-26] Many Studies have shown that the non-HDL-c being analogous to Apo-B in assessing atherogenic cholesterol and lipoprotein burden.[27] Although apo B can be measured directly but the measurement of non HDL cholesterol is more practical, reliable and inexpensive and is accepted as a surrogate marker for apoB in routine clinical practice [28].In diabetic patients it may be Insulin deficiency that causes increased metabolism of free fatty acid that may lead to disorder in lipid metabolism and stimulates protein kinase-C pathway. All these impair the vasodilatory response and hence predict the cardiovascular disease. The increase in triacylglycerol level may be due to the accumulation of triacylglycerol, increased lipogenesis and decreased fatty acid oxidation. Insulin resistance causes more catabolism of HDL particles and formation of LDL particles, this may lead to increase in LDL and decrease in HDL levels in type 2 diabetes. [29] Lipid ratios and AIP have been reported to indicate atherogenic dyslipidemia. Various lipid and lipoprotein fractions were shown to be associated in diabetes with and without complications. Researchers in their study observed that the atherogenic index and TC/HDL-c levels were significantly higher in diabetic patients than in controls and both these were found to be lowered in patients on treatment with insulin.[30] These findings suggest the role of lipid ratios in identifying the CV risk rather than the individual lipids alone.

Conclusion

In Diabetes, the alteration in the utilization of lipids and lipoproteins takes place that may induce atherogenic dyslipidemia and it is one of the most common risk factor for the development of atherosclerosis. Primarily, Low density lipoprotein cholesterol is used as the marker of cardiovascular risk in diabetes. Lipid ratios, atherogenic coefficient and atherogenic index of plasma have been found to indicate an atherogenic risk and are better predictors of cardiovascular risk than lipids alone. Hence all these parameters can be included in routine cardiac profile as the predictor of atherosclerotic damage.

References

1. Bennett PH, Knowles WC. Definition, diagnosis and classification of diabetes mellitus and glucose homeostasis. Smith, Josln's Diabetes Mellitus. 14th edition. Boston: Ovid Technologies, Inc 2005;331-3.
2. Klause G .Parhofer. Interaction between Glucose and Lipid Metabolism: More than Diabetic Dyslipidemia. *Diabetes Metab J* 2015;39(5):353–62.
3. Emerging Risk Factors Collaboration, Sarwar N, Gao P, Kondapally Seshasai SR, Gobin R, Kaptoge S, Angelantonio ED et al..Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *The Lancet* 2010;375(9733):2215–22.
4. Misra A, Khurana L. Obesity-related non-communicable diseases: South Asians vs White Caucasians. *Int J Obes (Lond)* 2011;35:167-87.
5. Abbasi MA, Hafeezullah N, Shah A, Abro AU, Sammo JA. Non-high density lipoprotein cholesterol and type 2 diabetes mellitus. *Pak J Physiol* 2007;3(2):1-4.
6. Peters AL. Clinical relevance of non-HDL cholesterol in patients with diabetes. *Clin Diabetes*. 2008;26:3–7.
7. Acay A, Ulu MS, Ahsen A, Ozkececi G, Demir K, Ozuguz U, et al. Atherogenic index as a predictor of atherosclerosis in subjects with familial mediterranean fever. *Medicina*. 2014;50(6):329-33.
8. Niroumand S, Khajedaluae M, Khadem-Rezaiyan M, Abrishami M, Juya M, Khodae G, et al. Atherogenic index of plasma (AIP): a marker of cardiovascular disease. *Med J Islam Repub Iran* 2015;29(1):627-35.
9. Onat A, Can G, Kaya H, Hergenc G. Atherogenic index of plasma” (log10 triglyceride/high-density lipoprotein cholesterol) predicts high blood pressure, diabetes, and vascular events. *J Clin Lipidol* 2010;4(2):89–98.
10. Zhan Y, Xu T, Tan X. Two parameters reflect lipid-driven inflammatory state in acute coronary syndrome: atherogenic index of plasma, neutrophil-lymphocyte ratio. *BMC Cardiovasc Disord* 2016;16(1):96.
11. Dobiasova M. AIP--atherogenic index of plasma as a significant predictor of cardiovascular risk: from research to practice. *Vnitr Lek* 2006;52:64-71.
12. Dobiasova M, Frohlich J, Sedova M, Cheung MC, Brown BG. Cholesterol esterification and atherogenic index of plasma correlate with lipoprotein size and findings on coronary angiography. *J Lipid Res* 2011;52(3):566-71.
13. Singh PS, Sharma H, Zafar KS, Singh PK, Yadav SK, Gautam RK, et al. Prevalence of type 2 diabetes mellitus in rural population of India- a

- study from Western Uttar Pradesh. *Int J Res Med Sci* 2017;5(4):1363-7.
14. Leon BM, Maddox TM. Diabetes and cardiovascular disease, epidemiology, biological mechanisms, treatment recommendations and future research. *World J Diabetes* 2015 10; 6(13): 1246-58.
 15. Vinik AI, Erbas T, Casellini CM. Diabetic cardiac autonomic neuropathy, inflammation and cardiovascular disease. *J Diabetes Investig* 2013;4(1):4-18.
 16. Palem SP, Abraham P. Atherogenic Index of Plasma an Indicator for Predicting Cardiovascular Risk in Addition to Endothelial Dysfunction in Type 2 Diabetic Subjects. *Journal Clin Diag Res* 2018;12(6):BC21-BC24.
 17. Trimbake SB, Prachi S, Chikhalikar, Pratinidhi SA. Comparative analysis of atherogenic index of plasma and body mass index in type II diabetes mellitus patients. *EJBPS* 2018;5(8):256-61.
 18. Muralidhara KCS, Hemantha KDS, Vishwanath HL. Role of non- HDL cholesterol in type II diabetes mellitus. *Int J Clin Biochem Res* 2018; 5(4):642-5.
 19. Butt M, Ali AM, Bakry MM. Lipid profile patterns and association between glycated haemoglobin (HbA1C) and atherogenic index of plasma (AIP) in diabetes patients at a tertiary care hospital in Malaysia. *Int J Pharm Pharm Sci* 2017;9(6):150-4.
 20. Nwagha UI, Ikekpeazu EJ, Ejezie FE, Neboh EE, Maduka IC. Atherogenic index of plasma as useful predictor of cardiovascular risk among postmenopausal women in Enugu, Nigeria,” *African Health Sciences* 2010;10(3):248–52.
 21. Du EM, Ukwamedu HA, Oghagbon ES. Assessment of Cardiovascular Risk indices in Type 2 Diabetes Mellitus. *Trop Med Surg* 2015; 3(2):1-4.
 22. Nimmanapalli HD, Kasi AD, Devapatla PK, Nuttakki V. Lipid ratios, atherogenic coefficient and atherogenic index of plasma as parameters in assessing cardiovascular risk in type 2 diabetes mellitus. *Int J Res Med Sci* 2016;4(7):2863-9.
 23. Ormazabal V, Nair S, Elfeky O, Aguayo C, Salomon C, Felipe A. Association between insulin resistance and the development of cardiovascular disease. *Cardiovasc Diabetol* 2018;17:122.
 24. Safo AS. Correlation between non-high-density lipoprotein-cholesterol and the degree of glycemic control in type 2 diabetes mellitus. *Med J Babylon* 2018;15(2):169-73.
 25. Kumpatla S, Soni A, Narasingan SN, Viswanathan V. Presence of elevated non-HDL among patients with T2DM with CV events despite of optimal LDL-C – A report from South India. *Indian heart Journal* 2016;68(3):378-9.
 26. Zabeen S, Rahman MR, Mustafa TG, Eusufzai NH, S Shermin S. Non-HDL Cholesterol and Type 2 Diabetes Mellitus. *AKMMCJ* 2012;3(2):15-8.
 27. Hermans MP, Sacks FM, Ahn SA, Rousseau MF. Non-HDL-cholesterol as valid surrogate to apolipoprotein B100 measurement in diabetes: Discriminant Ratio and unbiased equivalence. *Cardiovasc Diabetol* 2011;28(10):20.
 28. Anie LP. Clinical Relevance of Non-HDL Cholesterol in Patients with Diabetes. *Clinical Diabetes* 2008;26(1):3-7.
 29. Trimbake SB, Chikhalikar PS, Pratinidhi SA. Comparative analysis of atherogenic index of plasma and body mass index in type ii diabetes mellitus patients. *EJBPS* 2018;5(8):256-61.
 30. Siddiqui IA, Mariya LB, Rao JR. Lipid indices in type II diabetes mellitus and their association with macro and micro vascular complications. *Int J Med J Res Health Sci* 2013;2(1):87-92.

Source of Support: Nil

Conflict of Interest: Nil