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# A CORRELATIONAL ANALYSIS OF CARDIAC AUTONOMIC NEUROPATHY, ARTERIAL STIFFNESS, AND LIPID PROFILE IN DIABETIC PATIENTS.

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## Abstract

**Objective:**

It is necessary to comprehend the mechanistic connections between cardiovascular risk factors. This is the foundation for the present investigation.

**Materials and Methods:**

In the cross-sectional and observational research, patients with T2DM aged 53 to 62 years and age- and gender-matched healthy control subjects were recruited (n = 30 each, eight women). After obtaining the participants' consent, anthropometric measurements, physiological parameters including resting heart rate, peripheral blood pressure (PBP), central blood pressure (CBP), augmentation index% (AIx%), brachial-ankle pulse wave velocity, and lead II ECG for analysis of heart rate variability parameters were obtained. In addition, the lipid profile and fasting blood glucose were evaluated.

**Results:**

In T2DM patients, peripheral systolic blood pressure was significantly higher (P = 0.05). Patients with T2DM demonstrated dyslipidemia. In T2DM patients, the atherogenic index of plasma (AIP) was also significantly higher. The AIP index was discovered to have a negative association with HF. Multiple regression analysis identifies serum TG, high-density lipoprotein cholesterol (HDL-C), and AIP index as independent predictors of T2DM vasculopathy.

**Conclusion**:

Atherogenic dyslipidaemia was observed in T2DM patients in conjunction with elevated serum levels of TG, VLDL-C, and decreased serum levels of HDL-C in the present study. In addition, the AIP index, a predictor of cardiovascular risk, was significantly greater in T2DM patients. In these patients, dyslipidaemia was discovered to be associated with dysregulation of the autonomic nervous system.

**Recommendation:**

Recommendations for the treatment of CAN include early optimization of blood glucose regulation to avoid or delay the development of CAN in people with T1DM.

***Keywords:*** Type 2 diabetes mellitus, Arterial stiffness, Cardiac autonomic neuropathy (CAN), Heart rate variability, Lipid profile, Submitted: 2023- 09-15, Accepted: 2023-09-22

## 1. Introduction:

Diabetes mellitus has evolved as one of humanity's greatest diseases. It is a metabolic disorder that incapacitates every organ system and, as a

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result, increases morbidity and mortality. The estimated global prevalence of diabetes is 463 million, with a projected increase to 642 million over the next 25 years [1, 2]. By 2040, the number of diabetic patients in India is expected to surpass 123,5 million [3]. The complex pathophysiology of type 2 diabetes mellitus (T2DM) gives birth to heterogeneous disease syndromes, but hyperglycaemia [1] lies at the core of its diverse presentations. Some undiagnosed patients manifest with long-term complications of untreated chronic hyperglycemia late in the course of their illness.

Prolonged hyperglycemia is a leading cause of diabetic microvascular and macrovascular complications [4, 7, 8]. Chronic hyperglycemia induces advanced glycation end products (AGEs) via non-enzymatic glycation, modifies intracellular signalling cascades (protein kinase C activation), and increases oxidative stress. All of these mechanisms interact and result in numerous structural and functional alterations of the vascular wall, resulting in the development of atherosclerosis [9]. Hyperglycemia also increases platelet aggregation, thrombus formation risk, and progression of atherosclerosis [10].

Cardiovascular autonomic neuropathy (CAN) is a common and severe complication of diabetes. [13] One-fifth of diabetic patients have definitive CAN. A diagnosis of CAN is associated with a 5-fold increase in mortality compared to diabetic patients without CAN, as well as an increased prevalence of asymptomatic myocardial ischemia and systolic and diastolic left ventricular dysfunction [14-16]. The correlation between CAN incidence and QT prolongation increases the risk of malignant arrhythmias and sudden cardiac mortality [17]. Arterial rigidity is recognised as a cardiovascular risk factor distinct from dyslipidemia. There are studies examining the association between T2DM and cardiac autonomic neuropathy, arterial rigidity as measured by PWV, and lipid profile in T2DM patients, particularly in the South Asian population [4, 8-10]. In addition, all of these studies emphasised the importance of conducting additional research in order to gain a deeper understanding of the mechanistic links between multiple cardiovascular risk factors. However, there is a lack of research in the literature that examines the relationship between all three components in T2DM patients. This study aims to fill this gap in the literature.

## 2. Materials and methods:

### *2.1. Study Design and Population:*

This was an observational and cross-sectional study. Thirty T2DM patients aged 53 to 62 years (n = 30, 22 males and 8 women) were recruited from the outpatient endocrinology department. T2DM was diagnosed in accordance with American Diabetes Association criteria. Excluded from the investigation were diabetic patients with a history of liver systemic disorder, autoimmune disease, or any endocrinological disorder affecting blood vessels or peripheral vascular disease. 28 participants in the study had been affected by the disease for 1–10 years, while two had been affected for 15 years. The current investigation recruited 30 age- and gender-matched controls (n = 30) through advertisement.

### *2.2. Statistical Analysis:*

Using the Shapiro–Wilk normality test, the distribution pattern of the data was evaluated. It was discovered that the data were not typi- cally distributed. The data were displayed using the median (interquartile range) format. Comparing differences between variables using the Mann–Whitney U-test. Spearman's correlation test was used to analyse the association between parameters. Using multiple linear regression analyses, the independent risk factors for diabetic vasculopathy were analysed. A two-tailed P-value < 0.05 was statistically significant. Using the appropriate statistical tools (SPSS software, version 20 SPSS, IBM Inc., Chicago, IL), the data were analysed.

## 3. Results:

This study included a total of 30 patients. At the initial stage a number of 95 patients were examined for eligibility, however 65 patients were excluded from this study due to not being eligible.

The analysis of anthropometric data on T2DM patients and age- and gender-matched controls did not reveal a statistically significant difference in BMI [Table 1].

Peripheral systolic blood pressure (PSBP) was considerably higher (P = 0.05) in T2DM patients compared to age- and gender-matched controls. T2DM patients had elevated serum TG (P = 0.023), very low-density lipoprotein cholesterol (VLDL-C) (P = 0.005), and AIP index (P = 0.01), as well as low serum HDL-C (P = 0.004). Patients with T2DM have substantially higher (P = 0.0005) fasting glucose levels than healthy controls.

A significant correlation between BMI and serum TG concentration was observed (r = 0.369, P = 0.024). AIx% was positively correlated with peripheral diastolic blood pressure (r = 0.331, P = 0.010), peripheral systolic blood pressure (r = 0.484, P = 0.0005), central diastolic blood pressure (r = 0.318, P = 0.013), and central systolic blood pressure (CSBP) (r = 0.511, P = 0.0005). There was a significant positive correlation between AIP index and CSBP (r = 0.364, P = 0.031), baPWV (r = 0.353, P = 0.032), serum TG level (r = 0.894, P = 0.0005), serum LDL-C level (r = 0.371, P = 0.024), and serum VLDL-C level (r = 0.736, P = 0.0005). Intriguingly, the AIP index was found to have a negative correlation with HF (r = 0.388, P = 0.018). Multiple regression analyses have identified serum TG, HDL-C levels, and AIP index as independent predictors of T2DM vasculopathy that are statistically significant. There was no correlation between disease duration and physiological or biochemical parameters.

## 4. Discussion:

Thirty T2DM patients and the same number of age- and gender-matched controls participated in the current investigation. T2DM patients have substantially higher peripheral systolic blood pressure than age- and gender-matched controls. However, there was no significant difference between these study groups in terms of central systolic pressure and other markers of arterial rigidity. This may be attributable to the age-related alterations in the vasculature of the control group, as well as the medication intake of T2DM patients. Various factors, including age, gender, height, heart rate, and vasculature-affecting disease, are known to influence systolic pressure amplification [13]. In addition, T2DM patients were found to have dyslipidaemia, as evidenced by substantially elevated serum TG, VLDL-C, and low serum HDL-C levels in comparison to controls. This finding supports previous research [4].

In recent decades, the prevalence of T2DM has increased significantly among the Asian population. Moreover, a greater proportion of youthful and middle-aged individuals suffer from this condition, resulting in a significant socioeconomic burden for the nation. Increasing prevalence of T2DM increases the incidence of micro and macrovasculopathy in patients. However, few investigations have attempted to estimate the vascular status of T2DM patients systematically. Patients with type 2 diabetes were evaluated for arterial rigidity, cardiac autonomic neuropathy, and lipid profile.

There is abundant evidence in the scientific literature that an elevated serum level of LDL-C significantly contributes to the development of cardiovascular disease. In contrast, the present study revealed a combination of elevated serum levels of TG and VLDL-C and decreased serum levels of HDL-C. Frequently, atherogenic dyslipidaemia is accompanied by a combination of elevated TG and decreased HDL-C levels. In addition, multiple studies have shown that elevated serum TG levels are associated with an increased risk of cardiovascular disease. This association may be explained by the release of an inordinate amount of free fatty acid, the synthesis of pro-inflammatory cytokines, coagulation factors, and the impairment of fibrinolysis [14, 15].

AIP, calculated as the logarithm of the ratio of TG and HDL-C, was also substantially higher in T2DM patients than in control subjects. This result is also consistent with the results of the previous study [5]. Furthermore, the present study validates the notion that AIP may be used as a simple-to-calculate parameter to assess vascular

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Table 1: **Comparison of BMI and biochemical parameters**

| Variables | Control | T2DM |
|---|---|---|
| BMI (kg/m$^2$) | 25.01 | 26.02 |
| Serum HDL (mg/dL) | 47.9 | 39.9 |
| Serum fasting blood glucose (mg/dL) | 89.9 | 129.8 |
| AIP | 0.08 | 0.12 |
| Serum TG (mg/dL) | 108.7 | 147.9 |
| Serum VLDL (mg/dL) | 20.6 | 30.6 |
| Serum LDL (mg/dL) | 123.9 | 135.6 |
| Serum cholesterol (mg/dL) | 165.8 | 202.8 |

risk in T2DM patients [5]. AIP reflects plasma lipoprotein composition and is considered a predictor of atherosclerosis and cardiovascular risk. AIP values below 0.11 have been associated with a low cardiovascular disease risk, values between 0.11 and 0.24 with an intermediate risk, and values exceeding 0.24 with a high risk [15]. Based on AIP value, T2DM patients were found to have an intermediate cardiovascular risk in the present study [Table 1].

In the present study, the significant correlation between BMI and serum TG may be explained by the availability of excess free fatty acid from the adipose depot. In addition, a robust positive correlation was found between AIP index and CSBP and baPWV. Plasma atherogenicity is thought to be predicted by AIP. Therefore, the likelihood of arterial rigidity increases as AIP increases. In this study, there was no significant difference in arterial rigidity parameters between healthy controls and T2DM patients.

Given the age cohort of both control and T2DM patients, the age-associated changes in arterial stiffness cannot be ignored. AIP index was also found to be associated with lipid profile parameters. This result is to be anticipated given that the AIP index reflects metabolic interaction within the lipoprotein complex [16]. In this study, the AIP index was revealed to be negatively associated with HF (nu). However, there was no statistically significant difference in HF (nu) value between healthy controls and patients with T2DM.

HF (nu) represents the autonomic nervous system (ANS) parasympathetic limb. The abnormal lipid metabolism of T2DM patients may impair the normal functioning of the autonomic nervous system (ANS). It is plausible that dyslipidaemia may have a negative impact on the myelination status of the nerves, resulting in dysregulation of the autonomic nervous system [17, 18]. AIP index was also positively associated with noninvasive surrogate markers of arterial rigidity, CSBP and baPWV. Enhanced plasma atherogenicity may logically increase arterial rigidity. In the present study, a correlation between AIx%, another non-invasive surrogate marker of arterial rigidity, and PBP and CBP was observed. This observation leads to the conclusion that increased arterial rigidity may increase the likelihood of developing hypertension.

In the present study, multiple regression analysis identified serum TG, HDL-C levels, and AIP index as significant independent predictors of diabetic vasculopathy. This study demonstrates the advent of AIP as a screening parameter for determining vascular risk in T2DM patients. The sample size of the current investigation is a limitation. Consequently, the study's findings cannot be generalised. In addition, this was a cross-sectional and observational study. Accordingly, no cause-and-effect relationship can be established based on this study. Nonetheless, the present study's findings emphasise the importance of early assessment of T2DM patients for arterial stiffness and cardiac autonomic neuropathy in addition to serum lipid profile estimation.

## 5. Conclusion:

Compared to the control group, T2DM patients were found to have higher serum levels of TG and VLDL-C and lower serum levels of HDL-C in the current study. This finding indicates that T2DM patients have atherogenic dyslipidemia. In addition, the AIP index, a predictor of atherosclerosis and cardiovascular risk, was substantially elevated in T2DM patients. All of these observations indicate that diabetic patients have an increased cardiovascular risk. In T2DM patients, the AIP index was found to be negatively correlated with one of the activation parameters of the parasympathetic nerve. In patients with dyslipidaemia, myelination of the nerves may be affected, leading to dysregulation of the autonomic nervous system (ANS). A positive correlation between non-invasive surrogate markers of arterial stiffness and PBP and CBP suggests that increased arterial stiffness may increase systemic arterial pressure. Along with serum lipid profile estimation, early screening of T2DM patients for arterial rigidity and cardiac autonomic neuropathy may be advised.

## 6. Limitations:

The limitations of this study include a small sample population who were included in this study. The findings of this study cannot be generalized for a larger sample population.

## 7. Recommendation:

Recommendations for the treatment of CAN include early optimization of blood glucose regulation to avoid or delay the development of CAN in people with T1DM.

## 8. Acknowledgement.

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## 9. List of abbreviations:

T2DM- Type 2 Diabetes Mellitus
PBP- peripheral blood pressure
PSBP- Peripheral systolic blood pressure
CBP- central blood pressure
CSBP- central systolic blood pressure
AIx- augmentation index
ECG- Electrocardiogram
AIP- atherogenic index of plasma
HF- Heart failure
TG- triglyceride
HDL-C- high-density lipoprotein cholesterol
VLDL-C- Very-low-density lipoprotein Cholesterol
CAN- Cardiovascular autonomic neuropathy
T1DM- Type 1 Diabetes Mellitus
AGEs- advanced glycation end products
PWV- Pulse Wave Velocity
SPSS- Statistical Package for Social Sciences
BMI- Body Mass Index
LDL- low-density lipoprotein
ANS- autonomic nervous system

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## 11. Conflict of interest:

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