CARDIAC AUTONOMIC NEUROPATHY AND MICROALBUMINURIA IN TYPE 2 DIABETES MELLITUS- A CROSS-SECTIONAL ANALYSIS

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ABSTRACT

BACKGROUND

Autonomous neuropathy is one of the least focused complications of type 2 diabetes mellitus in clinical practice. CAN is a significant cause of morbidity and mortality associated with a high risk of cardiac arrhythmias and sudden death. Higher urinary albumin excretion has been suggested as a predicting diabetic nephropathy. This cross-sectional study sought to determine relationship of CAN with early renal decline in type 2 diabetes mellitus.

MATERIALS AND METHODS

Over a period of two years, patients with type 2 diabetes mellitus after careful exclusion of other risk factors for proteinuria, 199 patients were included in this cross-sectional survey. CAN was measured by portable ANSiscope and 24-hour urine microalbumin level was estimated. Correlation was sought between the two variable.

RESULTS

Out of the 199 patients chosen for the study, 127 were male. The mean age of diabetes was 6.4±3.9 years. 57.8% had late or advanced CAN and there was a significant linear correlation with 24-hour urine microalbumin levels.

CONCLUSION

Measurement of CAN is an effective way to assess the level of cardiac sympathetic dysfunction due to disease in patients with type 2 diabetes mellitus of more than 5 years duration. Urine microalbumin levels correlate with the degree of CAN. There is a strong need to conduct more studies about CAN to fully understand its pathology and develop treatment strategies to reduce cardiac mortality.

KEYWORDS

Cardiac Autonomic Neuropathy (CAN), Microalbuminuria, Type 2 Diabetes Mellitus.

BACKGROUND

Type 2 diabetes mellitus is widely prevalent in India and has a significant effect on health as well as the economy, particularly when the disease is associated with complications. Chronic complications often tend to be ignored by the patients as well as the treating doctors when diabetic care is implemented. Currently, testing for complications is an expensive and arduous in India. Hence, complications like neuropathy receive less concern in the care of the patient.

Cardiac Autonomic Neuropathy (CAN) is an often overlooked and common complication of diabetes mellitus.[1] The pathogenesis of CAN is complex and involves different pathways activated by hyperglycaemia that result in neuronal ischaemia and ultimately cell death. CAN can be subclinical in the initial years before and after the diagnosis of diabetes until the patient starts to develop resting tachycardia, exercise intolerance, postural hypotension and cardiac dysfunction.[2] Autonomic dysfunction is already present in patients with newly-diagnosed diabetes.[3] The most common and most prominent clinical feature of autonomic dysfunction is orthostatic hypotension. Cardiovascular Autonomic Nerve Function Testing (AFT) using heart rate variability is sensitive, noninvasive and

reproducible; therefore, it is easily applicable for screening a large number of diabetic patients even as outpatients.[4]

CAN was independently associated with Chronic Kidney Disease (CKD), albuminuria and reduced Estimated Glomerular Filtration Rate (eGFR) in patients with type 2 diabetes.[5] The ANSiscope™ device is a portable machine that provides the fundamental heart rate variability functions such as autonomic dysfunction, ANS monitoring and the 30:15 ratio test.[6] The ANSiscope™ device operates in real-time and is compliant with the following standards-

- IEC 60601-1.
- IEC 60601-1-2.
- IEC 60601-2-27.
- FDA approved.

The ANSiscope™ display features a 5-minute measurement. The healthy person has a balance that tends towards the parasympathetic predominance. The patient with advanced Diabetic Autonomous Neuropathy (DAN) shows a sympathetic predominance. This also suggests there is a reduced parasympathetic activity in the patients with advanced disease. The ANSiscope™ in diabetic patients can give us a very early indication of the autonomic dysfunction and a diagnosis of DAN. It also helps to initiate the treatment of hyperglycaemia earlier. It will also help in the review of the patients.

Diabetic nephropathy is the leading cause of end-stage renal disease worldwide.[7] The prevalence of microalbuminuria has been reported as 36.3%[8] from India, 16.8%[9] in Saudi Arabia, 22.7%[10] in Hong Kong, 14.2%[11] in Iran and 29% in Pakistan.[12]

Microalbuminuria is often the first sign of renal dysfunction (nephropathy) in diabetes mellitus. Microalbuminuria in patients with type II diabetes is predictive of proteinuria detected clinically and leads to increased mortality.[13] The presence of albuminuria is a predictor of renal and cardiovascular risk in patients with type 2 diabetes and hypertension.[14] It has been hypothesised that autonomic neuropathy impairs the normal diurnal blood pressure pattern.[15] Microalbuminuria is defined as excretion of 30-300 mg of albumin per 24 hours.[16] Routine screening for microalbuminuria is an easy, inexpensive, predictive procedure for neuropathy in diabetes mellitus and can guide appropriate intervention, thereby minimising disease progression. This procedure is also proven to be cost effective.[17] Albuminuria can be reduced effectively by inhibitors of Renin-Angiotensin System (RAS) and is used widely in the treatment of proteinuria in type 2 diabetes mellitus. Although, 24-hour excretion has traditionally been the preferred gold standard of measurement, the albumin-creatinine ratio has been shown to be a similarly valid screening tool for diabetic nephropathy.

In our study, we aim to study the correlation between the autonomous dysfunction with microalbuminuria in patients with type 2 diabetes mellitus. This is based upon the evidence gathered in our literature review that CAN could be used to identify patients with type 2 diabetes who are at increased risk of rapid decline in eGFR,[18] so that preventative therapies might be intensified. The study was done with permission from the Scientific Research Committee and Institutional Ethics Committee.

AIMS AND OBJECTIVES
The aims of the study include-
- Detect the levels of microalbumin in the 24-hour urine sample and determine the DAN level of sympathetic impairment using the ANSiscope™ in the study population.
- Determine the correlation coefficient between the urine microalbumin levels and DAN levels, respectively with the duration of type 2 diabetes mellitus.
- Using a linear regression model, determine the correlation between the DAN levels and the urine microalbumin levels in the study population.

The objectives will include-
- Use the ANSiscope™ to determine treatment strategies to reduce cardiovascular complications in the diabetic patients.
- Use the 24-hour urine microalbumin level as a predictive parameter to predict cardiac autonomic dysfunction in diabetic patients.

MATERIALS AND METHODS
Over a period of more than two years from February 2014 to April 2016, we recruited fully informed and consenting patients with type 2 diabetes mellitus visiting the medicine outpatient clinic on Wednesdays and Saturdays for this cross-sectional study. A complete diabetic history was taken and presence of peripheral neuropathy was tested for by using a 5.07/10-g monofilament.

Inclusion Criteria
- All patients visiting the medical OP on Wednesday and Saturday from February 2014 to April 2016.

Exclusion Criteria
- Patients with stage 1 systemic hypertension or above.
- Patients with chronic (>3 months) use of medicines like calcium channel blockers, NSAIDs and diuretics.
- Patients with history of chronic infections (tuberculosis).
- Patients who are chronic alcohol consumers.
- Young pregnant females.

Patients were then screened for the presence of other risk factors for microalbuminuria like systemic hypertension (>140/90 mmHg) by measuring blood pressure on two separate occasions in clinic and averaging the values, drugs (like calcium channel blockers, thiazides, chronic NSAIDS, etc.), chronic infections by measuring the erythrocyte sedimentation rate (ESR; cut-off value 20 mm/hr.; 2 separate levels, one week apart), chronic alcoholism (using CAGE questionnaire) and pregnancy in reproductive age women (by UPT - card test).

After eliminating patients with the above conditions, the patients were requested to provide 24-hour urine samples and those with macroalbuminuria (>300 mg/24 hrs.) were eliminated from the study. Subsequently, using the ANSiscope by DyAnsys recording of the cardiac autonomous activity was measured. The values of DAN and urine microalbumin were then tabulated.
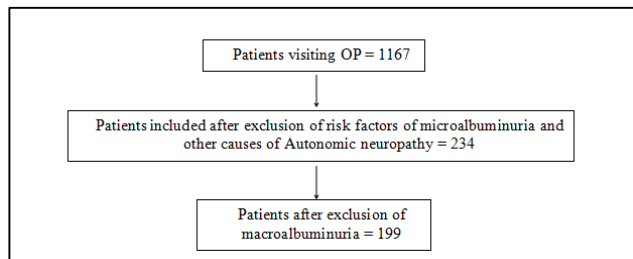

Chart Showing Selection of Patients

Statistical Analysis

We use correlation coefficient measurement (r value, $p<0.001$ with a 95% CI) for the values between the DAN levels and duration of type 2 diabetes mellitus. Similar correlation was sought for the measurement of microalbumin levels and duration of diabetes. For comparison between the DAN levels and urine microalbumin levels, we used a linear regression model of analysis using DAN levels as a dependent variable. An automatic weighted regression procedure using the equation $y=a+b \log (x)$ was used to find the F-ratio with a $p<0.0001$.

RESULTS

Out of the 1167 patients who visited the medicine outpatient clinic on the select days, 199 patients (mean age 58.4 ± 12.2) were recruited to the cross-sectional survey after careful exclusion of risk factors and macroalbuminuria. Out of them, 127 were males and all of them had a mean diabetic age of 6.4 ± 3.9 years. 66.4% of the patients were above the age of 55. 62.8% (n=125) had microalbuminuria (>30 mg/L). 23.6% of the study population had early DAN, 47.2% had late DAN and 10.6% had advanced DAN and significant sympathetic impairment.

There is a positive correlation between the DAN scores and duration of type 2 diabetes mellitus (correlation coefficient $r=0.9032$, $P<0.0001$ with a 95% confidence interval 0.8738 to 0.9259). There is also a positive correlation between microalbuminuria and duration of type 2 diabetes mellitus (correlation coefficient $r=0.8907$, $P<0.0001$ with a 95% confidence interval 0.8580 to 0.9163). The linear regression model with a sample size of 199 patients with the dependent variable of DAN and independent variable as urine microalbumin had a F-ratio of 1030 with a significant $p<0.0001$. The coefficient of determination R^2 was 0.8394 and the residual SD was 1.2476.
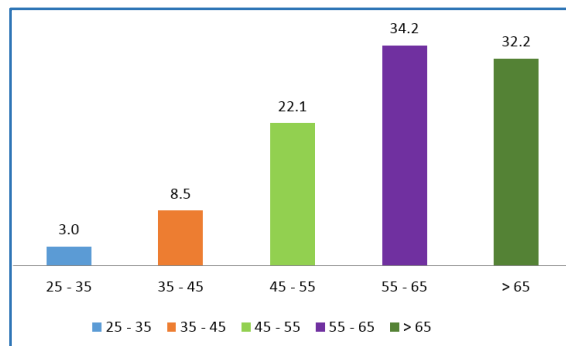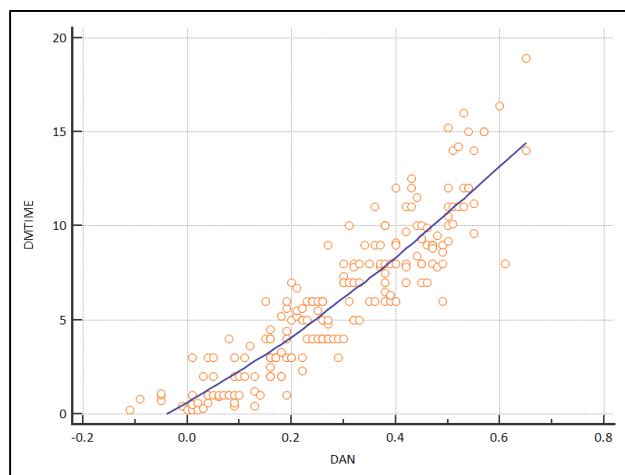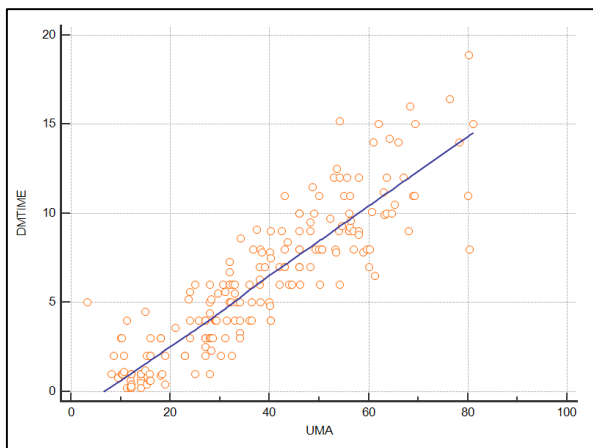

Figure 1. Distribution According to Age
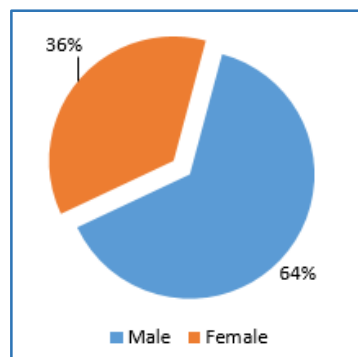
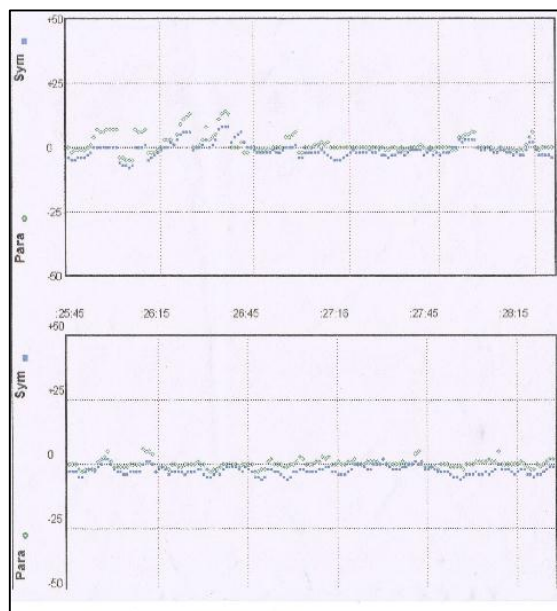**Figure 2. Distribution According to Sex**
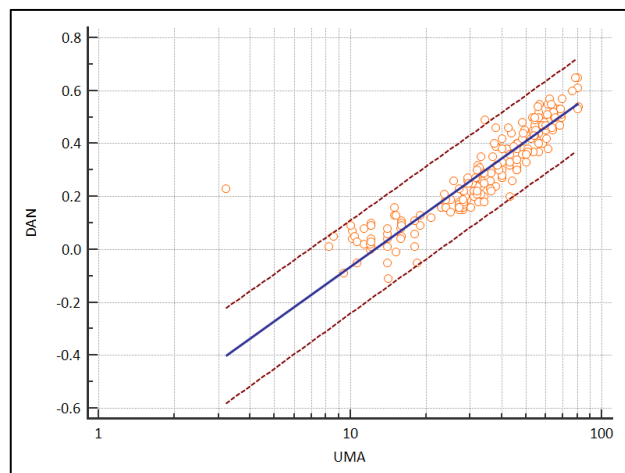
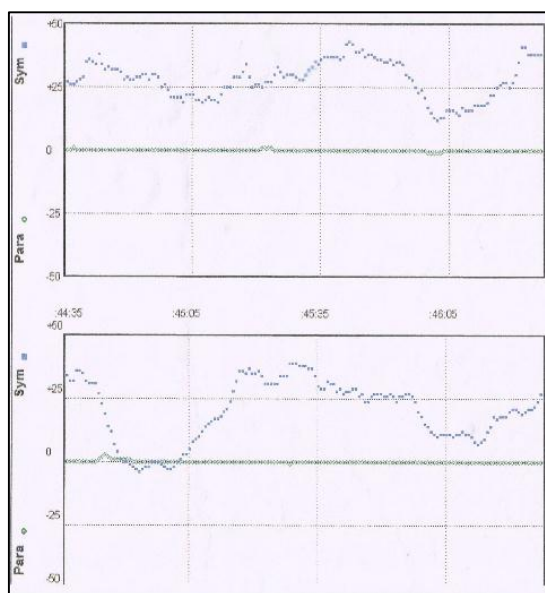**Figure 3. Linear Progression Analysis of DAN and Urine Microalbumin Level**

Figure 4. Correlation of DAN and Duration of Diabetes in Study Patients
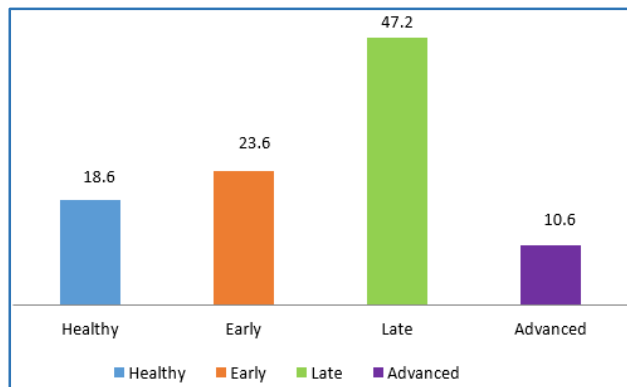
Figure 5. Correlation of Urine Microalbumin and Duration of Diabetes in Study Patients
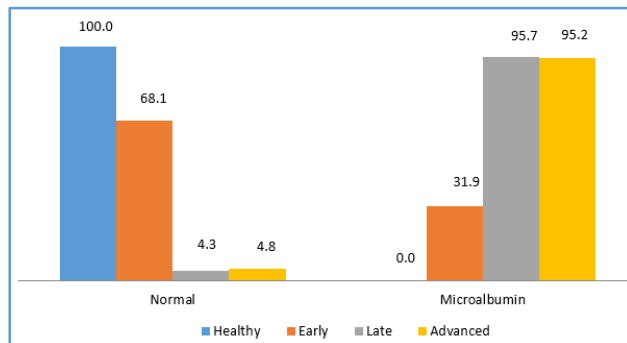

Figure 6. Cardiac Autonomic Dysfunction Shown by ANSiscope in Patient in Early Type 2 Diabetes Mellitus

Figure 7. Cardiac Autonomic Dysfunction Shown by ANSiscope in Patients with Longstanding Type 2 Diabetes Mellitus and having Raised Sympathetic Activity

Figure 8. Distribution According to DAN

Figure 9. Comparison of DAN Based on Urine Macroalbuminuria

DISCUSSION

In our study, we have proved that there exists a linear progression of CAN and microalbuminuria with the duration of diabetes in patients. Cross-sectional studies in young and middle-aged patients have found associations between diabetic cardiovascular autonomic neuropathy and microalbuminuria. Cardiovascular autonomic neuropathy and blood pressure are independently associated with microalbuminuria in older patients with type 2 diabetes.[19] Cardiovascular autonomic neuropathy has a prevalence of 17-22% in patients with type 1 and type 2 diabetes.[20] Impaired autonomic function is associated with all-cause and cardiovascular mortality. It is associated with microalbuminuria and with the progression of renal disease in adults.[18] Moreover, several authors have hypothesised that CAN is involved in the pathogenesis of diabetic nephropathy. Sympathetic overactivity has been shown to cause glomerular and tubular dysfunction in diabetic animal models via indirect (hypertension and angiotensin II) and direct insults.[21] So, cardiac autonomic dysfunction in patients already at risk (diabetes, hypertension or history of cardiovascular disease) maybe especially hazardous.[22] The association of mortality and cardiovascular autonomic dysfunction indicates that all individuals with abnormal autonomic function tests are candidates for close surveillance.[23] Intensified multifactorial intervention in all patients with type 2 diabetes and those with microalbuminuria will slow progression to nephropathy and progression of autonomic neuropathy.

CONCLUSION

These results indicate a strong and consistent association between CAN and microalbuminuria. Measurement of microalbumin levels in urine can predict the development of autonomic complications that may lead to cardiovascular mortality. Measurement of CAN is an effective way to assess the level of cardiac sympathetic dysfunction due to disease in patients with type 2 diabetes mellitus of more than 5 years duration. A 24-hour urine microalbumin is a proven method of assessing the microalbumin levels. CAN is more prevalent in patients with long-standing diabetes. There is a strong need to conduct more studies about CAN to fully understand its pathology and develop early treatment strategies to reduce cardiac mortality.

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