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Cardiovascular autonomic neuropathy and the impact on progression of diabetic kidney disease in type 1 diabetes

Theis Bjerre-Christensen, Signe A Winther, Nete Toft, Simone Theilade, Tarunveer S Ahluwalia, Maria Lajer, Tine W Hansen, Peter Rossing, Christian Stevns Hansen

ABSTRACT

Introduction We investigated the association between cardiovascular autonomic neuropathy (CAN) and decline in kidney function in type 1 diabetes.

Research design and methods We included 329 persons with type 1 diabetes. CAN was assessed by cardiovascular reflex tests (CARTs): heart rate response to deep breathing (E/I ratio), to standing (30/15 ratio) and to the Valsalva manoeuvre. Two or more pathological CARTs defined CAN diagnosis. Outcomes were yearly change in albuminuria or yearly change in estimated glomerular filtration rate (eGFR). An endpoint of eGFR decline >30%, development of end-stage kidney disease (ESKD) or death was examined.

Associations were assessed by linear and Cox regression.

Results Participants were aged 55.2 (9.4) years, 52% were male, with a diabetes duration of 40.1 (8.9) years, HbA1c of 7.9% (62.5 mmol/mol), eGFR 77.9 (27.7) mL/min/1.73 m², urinary albumin excretion rate of 14.5 (7–58) mg/24 hours, and 31% were diagnosed with CAN.

CAN was associated with a 7.8% higher albuminuria increase per year (95% CI: 0.50% to 15.63%, p=0.036) versus no CAN. The endpoint of ESKD, all-cause mortality and ≥30% decline in eGFR was associated with CAN (HR=2.497, p=0.0254).

Conclusion CAN and sympathetic dysfunction were associated with increase in albuminuria in individuals with type 1 diabetes suggesting its role as a potential marker of diabetic kidney disease progression.

INTRODUCTION

Type 1 diabetes is associated with an increased risk of developing microvascular complications such as retinopathy, nephropathy and neuropathy, along with macrovascular complications such as ischemic cardiovascular disease. Individuals with type 1 diabetes are at increased risk of renal complications due to presence of hyperglycemia and hypertension compared with healthy individuals. Diabetes is the leading cause of end-stage kidney disease (ESKD) in the USA. Chronic kidney disease (CKD) in diabetes or diabetic kidney disease (DKD) may be manifested as increased blood pressure, increased urinary albumin excretion rate (UAER) and decreased glomerular...
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filtration rate (GFR). Even mild degrees of DKD are associated with increased risk of death. Despite substantial improvements in glycemic control and management of other risk factors such as hypertension over the years, DKD prevention remains a challenge.

Presence of diabetic autonomic neuropathy, as measured using markers for cardiovascular autonomic neuropathy (CAN) is cross-sectionally and temporally associated with DKD. The prevalence of CAN in populations with diabetes ranges from around 20% and up to 65% in persons with longstanding diabetes. It has been shown that associations exist between CAN, especially increased sympathetic tone of the autonomic nervous system, and the development of DKD. It has also been suggested that CAN may be a part of the pathophysiology leading to DKD, or alternatively that the conditions occur together because of shared risk factors. Sympathetic dysfunction is seen early in the onset of CAN.

The objective of this study was to investigate the possible association between CAN, assessed by robust and internationally recognized indices, and future progression of DKD including increase in albuminuria, decline in renal function and a composite outcome comprising ESKD, all-cause mortality and ≥30% decline in estimated GFR (eGFR), in a cohort of persons with type 1 diabetes followed prospectively to allow identification of baseline risk markers of future progression of DKD.

**RESEARCH DESIGN AND METHODS**

This study is based on data from an original cohort of 900 participants with type 1 diabetes included in a case–control study at Steno Diabetes Center Copenhagen (conducted from 1993 to 2001). The cohort setup is described in depth previously. These subjects were recruited based on either longstanding normoalbuminuria (control) or DKD with persistent albumin excretion above 300 mg/24 hours in their history (cases). Of the 900 subjects in the original cohort, 571 were alive at the time of a cross-sectional and temporally analysis of their CAN status. CAN assessment included

Anthropometric, blood pressure and lifestyle measures

Height and weight were measured with light indoor clothing, without shoes, using a fixed rigid stadiometer (Seca, Chino, California, USA) and an electronic scale (Mettler Toledo, Glostrup, Denmark), respectively.

Oscillometric (UA787; A&D Medical, Abingdon, UK) office blood pressure was measured in a supine position after a 15-minute rest using an appropriate cuff size. Three measurements were obtained and averaged.

Lifestyle measures were obtained by questionnaires. Participants were classified as current smokers if they smoked ≥1 cigarette, cigar or pipe per day, and all others were classified as non-smokers. Physical activity was defined as being regularly physically active or not.

Biochemical measures

HbA1c was measured using high-performance liquid chromatography (Variant; Bio-Rad Laboratories, Munich, Germany) and serum creatinine concentration using an enzymatic method (Hitachi 912; Roche Diagnostics, Mannheim, Germany). UAER was measured in three consecutive 24-hour urine collections by an enzyme immunoassay. The CKD Epidemiology Collaboration Equation was used to calculate eGFR from plasma creatinine.

Endpoint assessment

Details on the assessment of endpoints have previously been published. Briefly, all participants were traced with no lost to follow-up in the Danish National Death and Health Registries on December 31, 2016. Information on cause of death was available until December 31, 2015. Participants were also traced in the electronic laboratory records for data on eGFR and urine albumin to creatinine ratio (UACR) obtained at regular outpatient visits.

Incident ESKD was defined as CKD stage 5 (International Classification of Diseases (ICD-10) N18.5), chronic dialysis (procedural code BJFD2), kidney transplantation (procedural code KKAS 00, 10, and 20), or eGFR <15 mL/min/1.73 m². The composite endpoint consisted of ESKD, >30% decline in eGFR from baseline, and all-cause mortality. The combined endpoint was included based on recent trends in larger studies to include this
specific composite endpoint. The yearly change in UACR was calculated based on all available measurements from outpatient visits during follow-up, in participants with at least two measurements and a minimum follow-up time of 3 years. Decline in eGFR was assessed as time to the first occurrence of ≥30% decrease from baseline without requiring confirmation and as yearly change in eGFR from available measurements from outpatient visits.

**Statistical analysis**
Characteristics are presented as means with SD, medians with IQRs, or as percentages depending on measurement

| Table 1 Baseline characteristics | No CAN estimation | No CAN estimation |
|----------------------------------|-------------------|-------------------|
|                                  | (n=181)           | (n=101)           |
| Men, n (%)                       | 86 (47.5)         | 57 (56.4)         |
| Age, years                       | 55.4 (9.7)        | 53.9 (7.7)        |
| HbA1c, mmol/mol                  | 60.9 (9.8)        | 66.3 (12.1)       |
| HbA1c, %                         | 7.7 (0.9)         | 8.2 (1.1)         |
| Body mass index, kg/m²           | 24.8 (3.7)        | 25.0 (4.4)        |
| Systolic blood pressure, mm Hg   | 131.0 (17.5)      | 136.7 (18.5)      |
| Diastolic blood pressure, mm Hg  | 74.1 (8.8)        | 74.8 (9.3)        |
| Diabetes duration, years         | 38.6 (8.6)        | 40.9 (8.3)        |
| Regular exercise, n (%)          | 136 (75.1)        | 64 (63.4)         |
| eGFR, mL/min/1.73 m²             | 84.4 (21.2)       | 63.9 (28.3)       |
| Urinary albumin excretion rate, mg/24 hours | 9.5 (6–24)  | 44.3 (13–314.0) |
| Microalbuminuria 30–300 mg/24 hours (n) | 21 (11)  | 27 (27)         |
| Macroalbuminuria >300 mg/24 hours (n) | 11 (6)  | 22 (22)         |
| LDL cholesterol, mmol/L          | 2.4 (0.7)         | 2.4 (0.7)         |
| Chronic kidney disease (CKD) classification category, n (%) | | |
| Normal: eGFR ≥90 mL/min/1.73 m² | 103 (56.9)        | 26 (25.7)         |
| Mild CKD: 60≥eGFR<90 mL/min/1.73 m² | 55 (30.4) | 29 (28.7)       |
| Moderate CKD: 30≥eGFR<60 mL/min/1.73 m² | 19 (10.5) | 32 (31.7)       |
| Severe CKD: 15≥eGFR<30 mL/min/1.73 m² | 4 (2.2)  | 11 (10.9)       |
| Kidney failure: eGFR <15 mL/min/1.73 m² | 0 (0)   | 3 (3.0)         |
| Medication, n (%)                |                  |                   |
| Beta-blockers                    | 13 (7.4)          | 20 (20.4)         |
| RAAS blockers                    | 176 (97.2)        | 97 (96)           |
| Statins                          | 93 (54.1)         | 72 (80.9)         |
| Autonomic function measures      |                  |                   |
| E/I ratio                        | 1.2 (1.1–1.3)     | 1.0 (1.0–1.1)     |
| 30/15 ratio                      | 1.1 (1.1–1.2)     | 1.0 (1.0–1.0)     |
| Valsalva maneuver                | 1.5 (1.4–1.8)     | 1.2 (1.1–1.3)     |
| SDNN, ms                         | 30.5 (20.5–42.5)  | 10.0 (7–15)       |
| Heart rate, beats/min            | 66.0 (10.6)       | 75.6 (12.2)       |

No CAN estimation: subject with one or no CAN measurements.
CAN, cardiovascular autonomic neuropathy; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; E/I ratio, expiration/inspiration ratio; LDL, low-density lipoprotein; RAAS, Renin–Angiotensin–Aldosterone System; SDNN, SD of normal to normal interval.
RESULTS

A total of 355 participants, of which 26 were outside the age range of validated CAN measurements (20–80 years of age), were eligible for the study (table 1). No subjects were excluded based on missing confounder variables. This left us with 329 subjects included in the analysis. At baseline, participants’ mean (SD) age was 55.2 (9.4) years, 52% were male, with diabetes duration of 40.1 (8.9) years, HbA1c of 62.5 (11.0) mmol/mol, 7.9%, eGFR 77.9 (27.7) mL/min/1.73 m², median (IQR) UAER of 14.5 (7.0–59.5) mg/24 hours and 31% were diagnosed with CAN. For subjects without CAN, 11 had macroalbuminuria, and 21 had microalbuminuria. For subjects with CAN, these numbers were 22 and 27, respectively. Median (IQR) follow-up time was 6.1 (5.8–6.5) years. During follow-up, 18 subjects died and 10 subjects developed ESKD. A total of 44 subjects reached the composite endpoint of ESKD, all-cause mortality or ≥30% decline in eGFR.

Yearly changes in eGFR were −0.73 mL/min/1.73 m² and −0.99 mL/min/1.73 m², respectively, for no CAN versus CAN group (p=0.54). Yearly changes in UACR were a 2% decrease and a 7% increase for no CAN versus CAN group (p=0.01), respectively.

In the adjusted model 5, participants with CAN had an increase in albuminuria of 7.80 percentage points per year (95% CI: 0.50 to 15.63, p=0.036) compared with subjects without CAN. There was no correlation between CAN status and change in eGFR in any model of adjustment (table 2).

CAN indices, CARTs and SDNN were analyzed with respect to yearly change in UACR and eGFR. In the unadjusted model, all indices of CAN were negatively associated to changes in UACR (online supplemental...
| Model 1 | N  | Parameter   | Outcomes | Estimate (95% CI)                           | P value |
|--------|----|-------------|----------|--------------------------------------------|---------|
|        | 141| Valsalva    | UACR     | −0.04 (0.02 to −0.07)                       | 0.031   |
|        | 144| Valsalva    | GFR      | 0.108 (−0.307 to 0.522)                     | 0.611   |
|        | 208| 30/15 ratio | UACR     | −0.04 (−0.07 to 0.0003)                     | 0.053   |
|        | 212| 30/15 ratio | GFR      | 0.058 (−0.271 to 0.387)                     | 0.730   |
|        | 211| E/I ratio   | UACR     | −0.04 (−0.07 to −0.01)                      | 0.010   |
|        | 215| E/I ratio   | GFR      | 0.215 (−0.149 to 0.588)                     | 0.247   |
|        | 213| SDNN        | UACR     | −0.04 (−0.07 to −0.003)                     | 0.047   |
|        | 217| SDNN        | GFR      | 0.171 (−0.228 to 0.57)                      | 0.401   |
| Model 2 | 141| Valsalva    | UACR     | −0.031 (−0.07 to 0.01)                      | 0.097   |
|        | 144| Valsalva    | GFR      | 0.057 (−0.364 to 0.478)                     | 0.790   |
|        | 208| 30/15 ratio | UACR     | −0.042 (−0.07 to −0.02)                     | 0.003   |
|        | 212| 30/15 ratio | GFR      | 0.050 (−0.276 to 0.376)                     | 0.763   |
|        | 211| E/I ratio   | UACR     | −0.039 (−0.07 to −0.01)                     | 0.014   |
|        | 215| E/I ratio   | GFR      | 0.222 (−0.145 to 0.589)                     | 0.234   |
|        | 213| SDNN        | UACR     | −0.034 (−0.068 to −0.001)                   | 0.054   |
|        | 217| SDNN        | GFR      | 0.156 (−0.243 to 0.554)                     | 0.444   |
| Model 3 | 141| Valsalva    | UACR     | −0.036 (−0.07 to 0.002)                     | 0.061   |
|        | 144| Valsalva    | GFR      | −0.118 (−0.538 to 0.303)                    | 0.582   |
|        | 207| 30/15 ratio | UACR     | −0.041 (−0.07 to −0.013)                    | 0.004   |
|        | 211| 30/15 ratio | GFR      | −0.046 (−0.366 to 0.274)                    | 0.779   |
|        | 210| E/I ratio   | UACR     | −0.031 (−0.064 to 0.002)                    | 0.069   |
|        | 214| E/I ratio   | GFR      | 0.003 (−0.376 to 0.382)                     | 0.988   |
|        | 212| SDNN        | UACR     | −0.03 (−0.07 to 0.05)                       | 0.090   |
|        | 216| SDNN        | GFR      | −0.084 (−0.484 to 0.315)                    | 0.679   |
| Model 4 | 141| Valsalva    | UACR     | −0.034 (−0.07 to −0.004)                    | 0.077   |
|        | 144| Valsalva    | GFR      | −0.034 (−0.447 to 0.378)                    | 0.870   |
|        | 205| 30/15 ratio | UACR     | −0.034 (−0.06 to −0.006)                    | 0.017   |
|        | 210| 30/15 ratio | GFR      | −0.025 (−0.350 to 0.301)                    | 0.882   |
|        | 208| E/I ratio   | UACR     | −0.016 (−0.05 to 0.017)                     | 0.344   |
|        | 213| E/I ratio   | GFR      | 0.037 (−0.361 to 0.435)                     | 0.855   |
|        | 210| SDNN        | UACR     | −0.018 (−0.05 to 0.02)                      | 0.322   |
|        | 215| SDNN        | GFR      | −0.045 (−0.460 to 0.369)                    | 0.830   |
| Model 5 | 129| Valsalva    | UACR     | −0.039 (−0.07 to −0.001)                    | 0.044   |
|        | 126| Valsalva    | GFR      | 0.120 (−0.318 to 0.558)                     | 0.591   |
|        | 185| 30/15 ratio | UACR     | −0.033 (−0.06 to −0.005)                    | 0.023   |
|        | 184| 30/15 ratio | GFR      | −0.057 (−0.395 to 0.282)                    | 0.742   |
|        | 185| E/I ratio   | UACR     | −0.018 (−0.053 to 0.017)                    | 0.317   |
|        | 184| E/I ratio   | GFR      | 0.008 (−0.424 to 0.439)                     | 0.972   |
|        | 187| SDNN        | UACR     | −0.021 (−0.06 to 0.017)                     | 0.262   |
|        | 186| SDNN        | GFR      | −0.186 (−0.625 to 0.253)                    | 0.406   |

Continued
In this cohort of 329 persons with type 1 diabetes, we found that presence of CAN was associated with progression in DKD when assessed by increase in albuminuria, but not with decline in renal function (eGFR). The analysis of the composite endpoint 30% decline in eGFR, kidney failure or death revealed an association with CAN status, whereby subjects with CAN had a higher risk of reaching the composite endpoint. These associations were independent of traditional risk factors for DKD including baseline \( HbA_1c \), UACR, eGFR and blood pressure.

Other studies have shown a similar association between CAN and decline in UACR for both persons with type 1 and 2 diabetes independent of other confounding factors such as glycemic control, blood pressure regulation and diabetes duration.\(^9\)\(^{11}\)\(^{13}\) In the current study, we demonstrated an association between CARTs primarily associated with sympathetic nervous function (Valsalva and 30/15 ratio) and future increases in albuminuria. Forsen \textit{et al.}\(^9\) previously demonstrated a correlation between E/I ratio and UACR, which was not apparent in our data although we could demonstrate an association with other CARTs.\(^9\) There was no significant association between any CART measures and changes in eGFR. CAN status (as examined using heart rate variability) has been reported to be associated with decline in eGFR, but not UACR in type 1 diabetes.\(^20\) In accordance with our findings, Lu \textit{et al.} found associations between CARTs and UACR, but not between CARTs and eGFR.\(^21\) Orlov \textit{et al.} found an association between CAN status and advanced progressive kidney failure defined as CKD stage ≥3 in a large cohort study of persons living with type 1 diabetes.\(^20\) The lacking associations between CAN and development of ESKD in our study may be due to a low number of cases.

DKD can be seen as consisting of two dimensions, a decline in eGFR, and an increase in albuminuria. Albuminuria is thought to be caused due to endothelial damage in the kidneys with glomerular leakage of albumin. A decline in eGFR is seen as a result of interstitial fibrosis in the kidneys. There is no direct correlation between albuminuria and eGFR, and as such, patients are capable of having one, without the other.\(^22\) An association between neuropathy and progression of DKD can be due to shared risk factors such as hyperglycemia. It has also been suggested that neuropathy is involved in the pathogenesis of DKD. CAN is associated with a lack of nocturnal dipping in blood pressure, which is related to a decline in kidney function.\(^23\) During the early stages of CAN, a decrease in cardiac autonomic parasympathetic tone and an increase in sympathetic tone are seen.\(^14\)
The increased activation of the sympathetic nervous system results in higher levels of circulating catecholamines, which results in higher blood pressure. This increase in blood pressure can lead to increased glomerular pressure, and in turn increased renal damage. The autonomic nervous system has a direct influence on the kidneys through input on the renal vasculature and juxtaglomerular apparatus. Longitudinal studies have shown that higher levels of circulating inflammatory factors may contribute to decline in kidney function. Exploring these possible mechanisms will lead to future studies. One might imagine a setup where the function of the sympathetic nervous system could be improved and the effect on the kidneys reduced, using vagal stimulation methods.

The national healthcare registries provide us with a rare opportunity for following persons throughout their life and treatment regime. This enables us to collect highly valid follow-up information. In this study, we have used the gold standard measurements to evaluate CAN by applying three internationally recommended CARTs.

Table 4: CAN and CARTs versus ESKD, all-cause mortality and ≥30% decline in eGFR from baseline

| Model | Events | Outcomes | HR (95% CI) P value |
|-------|--------|----------|---------------------|
| 1     | 44     | CAN      | 6.352 (3.268 to 12.346) <0.0001 |
|       | 44     | E/I ratio | 5.035 (2.487 to 10.193) <0.0001 |
|       | 26     | Valsalva  | 7.103 (3.163 to 15.951) <0.0001 |
|       | 43     | 30/15 ratio | 3.832 (2.045 to 7.179) <0.0001 |
| 2     | 44     | CAN      | 6.843 (3.493 to 13.404) <0.0001 |
|       | 44     | E/I ratio | 5.255 (2.586 to 10.677) <0.0001 |
|       | 26     | Valsalva  | 7.453 (3.278 to 16.945) <0.0001 |
|       | 43     | 30/15 ratio | 4.228 (2.218 to 8.060) <0.0001 |
| 3     | 44     | CAN      | 4.957 (2.410 to 10.194) <0.0001 |
|       | 44     | E/I ratio | 3.983 (1.856 to 8.545) 0.0004 |
|       | 26     | Valsalva  | 4.194 (1.582 to 11.117) 0.0039 |
|       | 43     | 30/15 ratio | 3.887 (1.905 to 7.933) 0.0002 |
| 4     | 44     | CAN      | 3.138 (1.472 to 6.690) 0.0031 |
|       | 44     | E/I ratio | 2.411 (1.077 to 5.4) 0.0324 |
|       | 26     | Valsalva  | 2.641 (0.975 to 7.159) 0.0562 |
|       | 43     | 30/15 ratio | 2.459 (1.165 to 5.194) 0.0183 |
| 5     | 39     | CAN      | 2.497 (1.119 to 5.571) 0.0254 |
|       | 39     | E/I ratio | 1.811 (0.776 to 4.226) 0.1693 |
|       | 24     | Valsalva  | 1.903 (0.668 to 5.421) 0.2284 |
|       | 43     | 30/15 ratio | 2.223 (0.990 to 4.990) 0.0529 |
| 6     | 23     | CAN      | 2.807 (0.874 to 9.014) 0.0829 |
|       | 23     | E/I ratio | 2.520 (0.600 to 10.585) 0.2070 |
|       | 23     | Valsalva  | 1.903 (0.769 to 5.673) 0.1373 |
|       | 23     | 30/15 ratio | 2.223 (0.493 to 3.775) 0.5496 |

Model 1: unadjusted. Model 2: adjusted for age and sex. Model 3: as model 2 and additionally adjusted for duration of diabetes, HbA1c, BMI, smoking, exercise, beta-blocker use, LDL cholesterol and systolic blood pressure. Model 4: as model 3, and additionally adjusted for baseline eGFR. Model 5: as model 4 and additionally adjusted for urinary albumin excretion rate. CARTs were evaluated as binary variables based on age-specific cut-off values.

BMI, body mass index; CAN, cardiovascular autonomic neuropathy; CARTs, cardiac autonomic reflex tests; eGFR, estimated glomerular filtration rate; E/I ratio, expiration/inspiration ratio; ESKD, end-stage kidney disease; LDL, low-density lipoprotein.
part of the autonomous nervous system, and as such, neither can be ruled out as an influencing factor.

Subjects with normoalbuminuria would not be expected to progress to ESKD, and persons with albuminuria might have already died from complications at the time of re-examination.

There was no correlation found between ESKD, eGFR >30% and CAN, hence the combined endpoint might be driven by all-cause mortality.

A sensitivity analysis of RAAS blockade was performed by additional adjustment for the use of these drugs. Some significant associations were lost. However, it is unclear whether RAAS can be considered a true confounder, as it is unclear whether it impacts both CAN measures and outcomes. RAAS blockade reduces the progression of DKD. However, it is not known if RAAS blockade confounds the possible effect CAN has on kidney disease. The results of RAAS adjustment may indicate that RAAS treatment could ameliorate the effect of CAN on kidney disease. However, such conclusions cannot be drawn due to confounding by indication. Hence, the focus of our analyses has been but on model 5.

Presence of CAN was a risk marker for progression of DKD, when assessed by longitudinal UACR measures and when a composite renal endpoint comprising ESKD, all-cause mortality and decline in eGFR ≥30% was applied, but not annual decline in eGFR, in persons with type 1 diabetes. These correlations were primarily driven by sympathetic nervous function at baseline. The current study identifies the association between CAN and progression of DKD in type 1 diabetes.

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