Cardiac autonomic neuropathy in patients with uraemia is not related to pre-diabetes

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ABSTRACT

INTRODUCTION: It has been proposed that pre-diabetes may cause neuropathy. The aim of this study was to investigate whether cardiac autonomic neuropathy (CAN) in uraemic patients was related to the presence of pre-diabetes.

MATERIAL AND METHODS: The study included 66 non-diabetic uraemic patients selected from a waiting list for kidney transplantation. They were on average 43 ± 12 years old, with a duration of uraemia of 32 ± 27 months in the pre-dialytic stage, or receiving either haemo-, or peritoneal dialysis. A control group of 14 healthy people matched by sex, age and body mass index were enrolled. Beat-to-beat variability was determined from the echocardiographic (ECG) recording during deep inspiration and expiration. CAN was defined as a beat-to-beat value below 10 beats/min. Pre-diabetes was defined as presence of impaired fasting glucose and/or impaired glucose tolerance measured by oral glucose tolerance test (WHO/American Diabetes Association criteria 2007).

RESULTS: The prevalence of CAN was 38% in uraemic patients compared with 8% in the controls ($p < 0.005$). Twenty-seven (41%) out of the 66 uraemic patients were pre-diabetic, while the remaining 39 had a normal glucose tolerance. The prevalence of CAN was comparable in uraemic patients with (44%) and without (33%) pre-diabetes). Uraemic patients with CAN were characterised by higher systolic blood pressure ($p < 0.05$) and higher age ($p < 0.005$) compared with uraemic patients without CAN.

CONCLUSION: The prevalence of CAN and impaired glucose tolerance is high in uraemic patients, but impaired glucose tolerance seems to play no significant role in the aetiology of CAN in uraemic patients.

Patients with end-stage renal disease independent of the presence of diabetes mellitus (DM) often have autonomic dysfunction [1]. Some of the earliest signs of autonomic neuropathy are a reduction in heart rate variability, the so-called beat-to-beat variation [2]. Abnormal beat-to-beat variation is both an independent risk factor for cardiovascular morbidity and for mortality in type I DM patients with nephropathy [3] and a risk factor for increased morbidity and mortality in chronic renal patients irrespective of their glucose status [4, 5]. The mortality of diabetic patients with cardiac autonomic neuropathy (CAN) has been reviewed [6]. Different methods and follow-up times were used, but the trend was clear: When CAN was present, the mortality rose three to six times over a five-year period compared with diabetic patients without CAN [6]. Most uraemic patients have some degree of insulin resistance, and patients with renal impairment often have abnormal glucose tolerance [7]. An increased prevalence of peripheral neuropathy is documented in persons with impaired glucose tolerance [8]. The aetiology of CAN is not known, either in diabetic or in uraemic patients. However, there are many theories about the pathophysiology underlying autonomic neuropathy, including metabolic nerve injury, neurovascular insufficiency, autoimmune damage or hyperglycaemia as a pathogenic factor [5]. Impaired glucose tolerance is a frequent finding in patients with painful sensory neuropathy and it has been proposed that impaired glucose tolerance may cause neuropathy [8]. If the glycaemic factors play a clinically significant role in the aetiology of autonomic neuropathy in uraemic patients, the presence of pre-diabetes (impaired glucose tolerance and/or impaired fasting glucose) must be associated with a higher prevalence of CAN compared with normoglycaemic patients.

In order to examine whether impaired glucose tolerance was a major component in the aetiology of CAN in uraemic patients, the present paper investigated whether CAN was associated with the presence of pre-diabetes in uraemic patients.

MATERIAL AND METHODS

Patients

All pre-dialysis, haemodialysis and peritoneal dialysis patients aged 18-65 years accepted for and awaiting kidney transplantation were screened between January 2006 and March 2008 at the regional transplantation centres at Rigshospitalet and Herlev Hospital. The exclusion criteria were a medical history of DM or DM diagnosed with an oral glucose tolerance test (OGTT). Out of 510 patients from the Scandia transplant waiting list for kidney transplantation, 140 patients fulfilled the inclusion criteria and were invited to participate. A total of 73 patients (52%), mostly Nordic Caucasians, accepted participation in the study. In all, seven (5%) were subse-

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TABLE 1

Clinical and glycaemic characteristics of uraemic patients classified according to glucose tolerance and a healthy control group.

	Uraemic patients		
	normal glucose tolerance (n = 39)	pre-diabetes (n = 27)	Healthy controls (n = 14)
Age, years, mean ± SD	41 ± 12	46 ± 12	39 ± 11
M/F, n	31/8	14/13[a,*]	9/5
BMI, kg/m^2, mean ± SD	25 ± 4	25 ± 4	24 ± 3
Waist-hip-ratio, mean ± SD	0.93 ± 0.09	0.90 ± 0.07	0.81 ± 0.08[b,***]
Ever smoker, n (%)	27 (69)	12 (44)	9 (64)
Dialysis and TX-status			
Haemodialysis, n (%)	25 (64)	13 (48)	–
CAPD, n (%)	11 (28)	12 (44)	–
Pre-dialysis, n (%)	3 (8)	2 (7)	–
ESRD, months, mean ± SD	31 ± 28	33 ± 26	–
Diagnoses, n (%)			
Glomerulonephritis	15 (39)	8 (30)	–
Hypertension	9 (23)	4 (15)	–
PKD	4 (10)	5 (19)	–
Vasculitis	1 (3)	1 (4)	–
Other/unknown	10 (26)	9 (33)	–
Antihypertensive drugs, n, mean (range)	2 (0-6)	2 (0-6)	–
Blood pressure, mmHg, mean ± SD			
Systolic	140 ± 21	144 ± 23	118 ± 10[b,***]
Diastolic	84 ± 14	85 ± 10	73 ± 8[b,***]
Beat-to-beat/min., mean ± SD (range)	13.1 ± 7.0 (4.8-30)	13.8 ± 6.7 (3.5-30)	23.8 ± 9.5 (6.8-41)[b,**]
Glycaemic status			
Fasting P-glucose, mmol/l, mean ± SD	5.1 ± 0.4	5.2 ± 0.4	5.0 ± 0.3
HbA_{1c}, %, mean ± SD	5.2 ± 0.3	5.3 ± 0.4	5.2 ± 0.2
P-glucose at 2-hours, mmol/l, mean ± SD	6.7 ± 1.0	8.8 ± 1.0[a,***]	5.4 ± 1.1[b,***]

BMI = body mass index; CAPD = continuous ambulatory peritoneal dialysis; ESRD = end stage renal disease; M/F = male/female; P = plasma; PKD = polycystic kidney disease; SD = standard deviation; TX = transplantation.

a) Normal glucose tolerance patients versus pre-diabetes patients: *) $p < 0.05$, ***) $p < 0.0005$.

b) Uraemic patients versus healthy controls: **) $p < 0.005$, ***) $p < 0.0005$.

Wilcoxon rank sum test or unpaired t-test were used where appropriate.

quently found to have DM by careful review of the patients' records (n = 4) or OGTT (n = 3). This left 66 uraemic patients without DM to be studied. A control group consisting of 14 healthy age, body mass index (BMI) and sex-matched subjects were recruited via public announcement.

The regional ethical committee (# KF 01279825) and The Data Protection Agency (#2006-41-5640) approved the study. All participants gave their informed written consent.

Study procedure

All participants were examined after an overnight fast including coffee, tobacco and exercise abstinence for ten hours. Usual antihypertensive medication was allowed in the morning.

Haemodialysis patients were examined between the days of haemodialysis. Peritoneal dialysis patients had peritoneal fluid drained in the morning at 6 a.m. The examination began between 8-11 a.m. After ten minutes of rest in the supine resting position, blood pressure was measured in triplicate from the arm opposite to a fistula or dialysis catheter. The mean arterial blood pressure was based on the mean of these three measurements. Fasting blood samples were drawn for determination of glucose, insulin and HbA_{1c} (**Table 1**).

All blood samples were drawn from an antecubital vein. Plasma glucose concentrations were analysed by the glucose-hexokinase method (Gluco-quant, Roche Diagnostics GmbH, D-68298 Mannheim, Germany) and insulin was measured using enzyme-linked immunosorbent assay kits (Elecsys, Roche Diagnostics GmbH, D-68298 Mannheim, Germany). All assays were automated and performed on a Cobas Fara robot (Roche Diagnostics GmbH, Mannheim, Germany). Standard laboratory methods were applied for the analysis of the other samples. The examiners were blinded with regard to the actual clinical and metabolic status of the patient at the time of examination and all clinical information was analysed and described after data collection had been completed.

ECG was recorded with the patient in the supine position during five respiratory cycles of each five seconds with maximum inspiration and expiration [9]. This respiration rate is reported to give the greatest effect of beat-to-beat variation [10]. For each respiratory cycle, the shortest and the longest RR interval was measured in every derivation on the ECG and the difference was then calculated and converted into beats/min. [9] (**Figure 1**).

$$\text{beats/min.} = \left(\frac{25\ \text{mm/s}}{\text{shortest interval (mm)}} \times 60\ \text{s/min.}\right) - \left(\frac{25\ \text{mm/s}}{\text{longest interval (mm)}} \times 60\ \text{s/min.}\right)$$

When a cycle was incomplete or immeasurable, an average value of the other metrics was calculated and used to calculate the beat-to-beat variability. In this study, CAN was defined as beat-to-beat variability < 10 beats/min. Information about patients' medication use, diagnosis and duration of their kidney disease was obtained from their records and by interview.

Oral glucose tolerance test

A 75-gram oral glucose tolerance test was performed according to the WHO/American Diabetes Association 2007 criteria [11]. We determined the prevalence of normal glucose tolerance (NGT: Fasting plasma glucose < 5.6 mmol/l and two-hour post load glucose < 7.8 mmol/l), impaired fasting glucose (IFG: Fasting plasma glucose between 5.6 and 6.9 mmol/l) and impaired

glucose tolerance (IGT: two-hour post load glucose between 7.8 and 11.1 mmol/l and fasting below 7.0 mmol/l) as well as pre-diabetes (IFG+IGT).

RESULTS

Pre-diabetes was present in 27 (25 IGT and two IGF) (41%) uraemic patients. Age, underlying renal disease, duration of dialysis treatment, dialysis method, smoking status, blood pressure and antihypertensive medication use were comparable in the uraemic patients with and without pre-diabetes (Table 1). The patients with pre-diabetes were characterized by a higher two-hour glucose value, but fasting plasma glucose and HbA_{1c} were comparable (Table 1).

The uraemic patients had a significantly higher incidence of CAN than the healthy control group (38% versus 8%, $p < 0.005$), but there were no differences between the uraemic patients with and without pre-diabetes (44% versus 33%, non significant, n = 27 versus n = 39).

Uraemic patients with abnormal beat-to-beat variation were significantly older ($p < 0.005$), had a higher systolic blood pressure ($p < 0.05$) and showed a tendency towards longer duration of uraemia than uraemic patients with a normal beat-to-beat variation (**Table 2**). Smoking habits, renal diagnosis, medication use and duration of dialysis treatment were comparable in uraemic patients with and without abnormal beat-to-beat variability (Table 2).

DISCUSSION

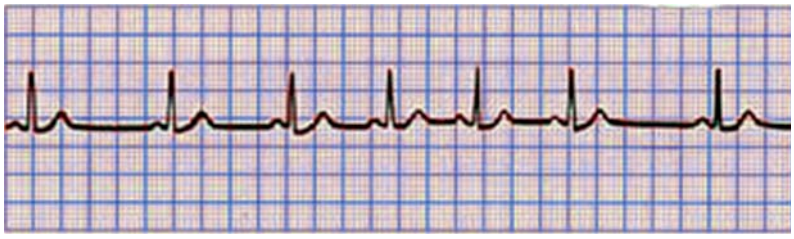
This paper is the first to demonstrate a comparable rate of CAN in uraemic patients with and without pre-diabetes. This finding suggests that impaired glucose tolerance is not a major component of the aetiology of CAN in uraemic patients.

In this study, we used a well-documented, non-invasive bedside method for determining CAN [9, 10]. The method is highly reproducible, requires only a few minutes of bed rest for the patient, is easy to perform and involves no discomfort for the patient [9]. We defined CAN as abnormal beat-to-beat variation < 10 beats/min. This is in accordance with the definition used in a recent study by Aastrup [3], where CAN was an independent predictor of fatal and non-fatal cardiac morbidity among patients with diabetic nephropathy. Beat-to-beat variation, as a measure of CAN, has been validated in numerous other studies [1, 3, 10, 12, 13], and a decline in beat-to-beat variation is one of the earliest signs of CAN [14].

The main reasons for patients' non-attendance were long travelling time or inability to use extra days at the clinic, in addition to the time already used for dialysis. In this context, we find that a participation rate of 52% is acceptable and we suggest that the findings are applicable to the whole population of uraemic patients suitable for transplantation.

FIGURE 1

Electrocardiography during respiratory cycles with maximal inspiration and expiration used for calculation of beat-to-beat variation.



The occurrence of CAN was more frequent with increased age and higher systolic blood pressure. This is in accordance with other studies, which have shown that beat-to-beat variation decreases with increasing age in both healthy and diabetic people [10] and in people with high blood pressure [15]. The use of β-blocker apparently did not influence the results since the use of β-blockers was comparable among the uraemic patients with normal glucose tolerance (46%) and the pre-diabetic patients (45%) and the use of β-blocker has not been described to affect heart rate variability [10, 16]. However, the onset of hypertension often precedes the diagnosis of diabetes, especially when insulin resistance and hyperinsulinaemia are present. In patients with early autonomic neuropathy, sympathetic overactivity stimulates the renin-angiotensin-aldosterone system activity, promotes sodium reabsorption and increases peripheral resistance, thus inducing hypertension [17]. Whether hypertension induces development of CAN remains speculative.

Hayano et al showed that in 31 patients treated with haemodialysis, abnormal beat-to-beat variation was associated with an increased mortality. Among the patients with a beat-to-beat variability of 22 beats/min at baseline, 67% had died within five years compared with 15% among patients with normal beat-to-beat variation [18]. The prevalence of CAN has been described to be higher among patients in peritoneal dialysis than in patients in haemodialysis [1], but our study could not confirm this finding.

The insulin-mediated glucose metabolism is reduced in ureamic patients mainly due to a reduced glucose uptake in the peripheral tissue [7, 19]. This insulin-resistant state contributes to the development of diabetes and pre-diabetes. Our findings of a higher hip-waist ratio and prevalence of pre-diabetes among the uraemic patients than among the control group correlates well with this fact [11].

TABLE 2

Clinical characteristics of uraemic patients with normal beat-to-beat measurement (≥ 10 beats/min.) and abnormal beat-to-beat measurement (< 10 beats/min.) and of a healthy control group.

	Normal (n = 41)	Abnormal (n = 25)	Healthy controls (n = 14)
Age, years, mean ± SD	39 ± 12	50 ± 11[a,**]	39 ± 11
M/F, n	28/13	17/8	9/5
BMI, kg/m^2, mean ± SD	25.2 ± 3.7	24.8 ± 3.5	24.0 ± 3.0
Waist-hip-ratio, mean ± SD	0.93	0.91	0.81
Ever smoker, n (%)	22 (54)	17 (68)	9 (64)
Dialysis and TX-status			
Haemodialysis, n (%)	21 (51)	17 (68)	–
CAPD, n (%)	15 (37)	8 (32)	–
Pre-dialysis, n (%)	5 (12)	0	–
ESRD, months, mean ± SD	27 ± 26	38 ± 27	–
Diagnoses, n (%)			
Glomerulonephritis	7 (17)	6 (24)	–
Hypertension	16 (39)	7 (28)	–
PKD	1 (2)	1 (4)	–
Vasculitis	7 (17)	2 (8)	–
Other/unknown	10 (24)	9 (36)	–
Antihypertensive drugs, n (%)			
0	2 (4.9)	2 (8)	–
1	10 (24.4)	8 (32)	–
2	9 (22)	3 (12)	–
3	17 (41.5)	5 (20)	–
4	2 (4.9)	4 (16)	–
5	1 (2.4)	2 (8)	–
6	0	1 (4)	–
Blood pressure, mmHg, mean ± SD			
Systolic	136 ± 17	151 ± 26[a,*]	118 ± 10[b,***]
Diastolic	83 ± 11	87 ± 14	73 ± 8[b,***]
Glucose status			
Pre-diabetes, n (%)	15 (37)	12 (48)	0[b,***]
Fasting P-glucose, mmol/l, mean ± SD	5.1 ± 0.5	5.1 ± 0.4	5.0 ± 0.3
P-glucose at 120 min., mmol/l, mean ± SD	7.5 ± 1.5	7.7 ± 1.4	5.4 ± 1.1[b,***]

BMI = body mass index; CAPD = continuous ambulatory peritoneal dialysis; ESRD = end stage renal disease; M/F = male/female; P = plasma; PKD = polycystic kidney disease; SD = standard deviation; TX = transplantation.

a) Patients with normal beat-to-beat versus patients with abnormal beat-to-beat: *) $p < 0.05$, **) $p < 0.005$.

b) Uremic patients versus healthy controls: ***) $p < 0.0005$.

Wilcoxon rank sum test or unpaired t-test were used where appropriate.

Women were more prevalent in the group with abnormal glucose metabolism than in the group with normal glucose metabolism, but other studies failed to demonstrate any association between female sex and the development of CAN [9, 20].

Unfortunately, we did not examine the patients' peripheral vibration sense threshold and are therefore unable to determine the incidence of peripheral neuropathy in this patient population. A study by Karamitsos found that diabetic autonomic neuropathy progresses rapidly over a two-year period after detection of a reduced beat-to-beat variability [14]. The uraemic patients in our study had end-stage renal disease for 31 ± 28 months if they had a normal glucose tolerance level and 33 ± 26 months if they had pre-diabetes. Elevated systolic pressure is common among uraemic patients and related to the presence of autonomic neuropathy. One may speculate whether intensification of the antihypertensive treatment or kidney transplantation may reduce the prevalence of CAN. At present, one study has suggested that cardiovascular autonomic dysfunction can be reversed by renal transplantation [4]. All the present patients are on a transplantation waiting list, and determination of the beat-to-beat variation after kidney transplantation could be of interest.

CONCLUSION

The prevalence of CAN and impaired glucose tolerance is high in uraemic patients, but impaired glucose tolerance seems to play no significant role in the aetiology of CAN in uraemic patients.

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LITERATURE

1. Hathaway DK, Cashion AK, Milstead J et al. Autonomic dysregulation in patients awaiting kidney transplantation. Am J Kid Dis 1998;32:221-9.
2. Pickup J, Williams G. Textbook of diabetes. In: Clinical features of neuropathy. 2nd ed. Cambridge: Blackwell Science, 1997: Vol. 2, Chapter 50.
3. Astrup AS, Hansen BV, Tarnov L et al. Cardiac autonomic neuropathy predicts cardiovascular morbidity and mortality in Type 1 diabetic patients with diabetic nephropathy. Diabetes Care 2006;29:334-9.
4. Robinson TG, Carr SJ. Cardiovascular autonomic dysfunction in uraemia. Kidney Int 2002;62:1921-31.
5. Retnakaran R, Zinman B. Type 1 diabetes, hyperglycaemia, and the heart. Lancet 2008;371:1790-9.
6. Vink AI, Maser RE, Mitchell BD et al. Diabetic autonomic neuropathy. Diab Care 2003;26:1553-79.
7. DeFronzo RA, Alvestrand A, Smith D et al. Insulin resistance in uraemia. The American Society for Clinical Investigation 1981;67:563-8.
8. Smith AG, Singleton JR. Increased prevalence of impaired glucose tolerance in patients with painful sensory neuropathy. Diab Care 2001;24: 1448-53.
9. Buus S, Hilsted J. Respiratorisk sinus arytmi (beat-to-beat variation) hos insulin behandlede diabetikere. Ugeskr Læger 1979;44:3028-31.
10. Zeuzem S, Olbrich HG, Seeger C et al. Beat-to-beat variation of heart rate in diabetic patients with autonomic neuropathy and in completely cardiac denervated patients following orthotopic heart transplantation. Int J Cardiol 1991;33:105-14.
11. American Diabetes Association. Diagnosis and classification of diabetic mellitus. Diab Care 2007;30:1:42-7.
12. Dyrberg T, Benn J, Christiansen JS et al. Prevalence of diabetic autonomic neuropathy measured by simple bedside test. Diabetologia 1981;20: 190-4.
13. Murray A, Erwing DJ, Campell IW et al. RR interval variations in young male diabetics. Brit Heart J 1975;37:882-5.
14. Karamitos DT, Didangelos TP, Athyros VG et al. The natural history of recently diagnosed autonomic neuropathy over a period of 2 years. Diabet Res Clin Pract 1998;42:55-63.
15. Studinger P, Lénárd Z, Mersich B et al. Determinant of baroreflex function in juvenile end-stage renal disease. Kid Internat 2006;69:2236-42.
16. Malik M, Bigger JT, Camm AJ et al. Heart rate variability – standards of measurement, physiological interpretation, and clinical use. Eur Heart J 1996;17:354-81.
17. Perin PC, Maule S, Quadri R. Sympathetic nervous system, diabetes and hypertension. Clin Exper Hypertens 2001;23:45-55.
18. Hayano J, Takahashi H, Toriyama T et al. Prognostic value of heart rate

variability during long-term follow-up in chronic haemodialysis patients with end-stage renal disease. Nephrol Dial Transplan 1999;14:1480-8.
19. Hornum M, Jørgensen KA, Hansen JM et al. New onset diabetes mellitus after kidney transplantation in Denmark. Clin J Am Soc Nephrol 20101;5:709-16.
20. Ziegler D, Rathmann W, Dickhaus T et al. Neuropathic pain in diabetes, prediabetes and normal glucose tolerance. The MONICA/KORA Augsburg Surveys S2 and S3. Pain Med 2009;10:393-400.