Pre-diabetes and arterial stiffness in uraemic patients

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Abstract

Background. In order to address factors of relevance for new onset diabetes mellitus and cardiovascular disease after kidney transplantation, we investigated the presence of pre-diabetes, arterial stiffness and endothelial dysfunction in patients with end-stage renal disease (ESRD) accepted for kidney transplantation.

Methods. Pre-diabetes and an insulin sensitivity index were estimated by an oral glucose tolerance test in 66 consecutive uraemic patients, without diabetes, being on the waiting list for the first renal transplantation. A control group consisted of 14 healthy subjects.

Arterial stiffness was measured by aorta pulse wave velocity (PWV) and aorta augmentation index (AIX). Endothelial function was evaluated by flow-mediated vasodilatation (FMD) and plasma concentrations of von Willebrand factor antigen (vWF). Mean arterial blood pressure (MAP) was measured in supine resting position.

Results. Twenty-seven uraemic patients (41%) had pre-diabetes (IFG+IGT), and 39 had normal glucose tolerance. The uraemic patients were more insulin resistant with lower insulin sensitivity index compared to healthy controls (6.1 ± 3 vs. 15 ± 7, P < 0.0001) but with no difference between patients with and without pre-diabetes. HbA1c and fasting plasma glucose was comparable in uraemic patients with and without pre-diabetes.

PWV was higher in pre-diabetic compared to normoglycaemic uraemic patients (9.1 ± 3 vs. 7.3 ± 2 m/s, P = 0.03) and healthy controls (9.1 ± 3 vs. 6.7 ± 1, P = 0.01), while AIX did not differ (24.9 ± 13 vs. 23.2 ± 12 vs. 17 ± 16, P = NS). Presence of pre-diabetes was positively associated to PWV in a univariate analysis. Multivariable analysis revealed age and MAP as independent predictors of PWV in uraemic patients. FMD and vWF were impaired in uraemic patients compared to healthy controls (3 ± 4 vs. 7 ± 3, P = 0.007 and 1.8 ± 0.7 vs. 0.96 ± 0.3 kIU/L, P = 0.0002, respectively) but with no difference between the two groups of uraemic patients. In conclusion, a high prevalence of pre-diabetes, impaired insulin resistance, increased arterial stiffness of aorta as well as impaired augmentation index and vasodilatation was demonstrated in uraemic patients prior to kidney transplantation. Increased arterial stiffness of aorta and augmentation index were independently associated with age and blood pressure.

Keywords: arterial stiffness; augmentation index; insulin resistance; pre-diabetes; pulse wave velocity

Introduction

New onset diabetes mellitus after solid organ transplantation is an important clinical challenge associated to increased risk of major cardiovascular events after transplantation [1,2]. Previous studies have focused on metabolic changes as they appear after transplantation, and the presence of pre-diabetes at baseline before transplantation has only been sparsely investigated [3,4]. However, especially in kidney transplant recipients, studies before transplantation are highly relevant since uraemic patients are characterized by increased insulin resistance. Pre-diabetes may therefore be prevalent in patients with end-stage renal disease (ESRD) [5–8] and potentially associated with vascular damage.

Arterial stiffness can be estimated by aorta pulse wave velocity (PWV) [9], which reflects damage of the elastic tissue of aorta. An increased PWV has been shown to be an integrated index of vascular risk factors [10]. It is associated with increased mortality in ESRD [3,11,12] and is associated with hypertrophy of the arterial walls [13] and arterial calcifications [14]. Arteries are stiffer in patients with type 1 and 2 diabetes with different degrees of diabetic and cardiovascular complications [15–17], and a potential association of impaired glucose tolerance or pre-diabetes with diminished arterial elasticity in pre-diabetes may exist. Thus, presence of pre-diabetes in ESRD patients may also be associated with further increased arterial stiffness leading to increased risk of cardiovascular events [18]. Similarly, increased pulse pressure is predic-
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tive of cardiovascular mortality in type 2 diabetes [19,20], and augmentation of the pulse pressure is, at least in part, secondary to increased stiffness of mainly the resistance arteries. It can be measured by applanation tonometry using the pressure waveform at the radial artery. Mathematically, it is transformed into the pressure waveforms in ascending aorta representing the true workload of the left ventricle [21].

Endothelial function measured by endothelium-dependent dilatatory response of the brachial artery has also been found to be impaired in both uraemia [22] and diabetes [23] and may reflect presence of vascular disease [24] or early vascular damage.

A relationship between presence of pre-diabetes and increased arterial stiffness and endothelial dysfunction may therefore be present in the uraemic population. We studied the presence of pre-diabetes, arterial stiffness and endothelial dysfunction in a group of non-diabetic patients with ESRD accepted for kidney transplantation. The aim was to determine the prevalence of pre-diabetes in uraemic patients prior to transplantation and to investigate the associations between pre-diabetes, arterial stiffness and endothelial dysfunction.

Materials and methods

Patients

All pre-dialysis, haemodialysis and peritoneal dialysis patients, aged between 18–65 years, accepted for and awaiting their first kidney transplantation were screened. Exclusion criteria were medical history of diabetes or diabetes diagnosed during oral glucose tolerance test (OGTT). The screening was conducted in the period between January 2006 and March 2008 at the regional transplantation centres at Rigshospitalet and Herlev Hospital. Out of 510 patients from the Scandiatransplant waiting list for kidney transplantation, 140 patients who fulfilled the inclusion criteria were invited to participate. Seventy-three patients (52%), mostly Nordic Caucasians, accepted participation in the study, of which 7 (5%) were found to have diabetes by careful review of the patients’ record (n = 4) or OGTT (n = 3), which left 66 uraemic patients without diabetes to be studied. The main reasons for non-attendance were long travelling time to the laboratory or inability to use extra days at the clinic besides the time already used for dialysis.

The participants were asked about previous diagnosis of diabetes, acute myocardial infarction and stroke, and the medical records were carefully reviewed for these diagnoses. A control group consisting of 14 healthy Caucasian, body mass index (BMI) and sex matched subjects was recruited from public announcing.

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 10 h. Usual antihypertensive medication was allowed in the morning.

Haemodialysis patients were examined between the days of haemodialysis, and peritoneal dialysis patients had the peritoneal fluid drained in the morning at 6 p.m. The examination began between 8 and 11 p.m. After 10 min of rest in the supine resting position, blood pressure was measured in triplicate from the arm opposite to a fistula or dialysis catheter. Mean arterial blood pressure (MAP) was based on the mean of these three measurements. Fasting blood samples were drawn for the determination of glucose, HbA1C, homocystein, von Willebrand factor antigen (vWF), haemato logical factors, lipids, urate, C-reactive protein and parathyroid hormone (PTH) (Table 3).

All blood samples were taken from an antecubital vein. Plasma glucose concentrations were analysed by the glucose-hexokinase method (Glucquan®, Roche Diagnostics GmbH, D-68298 Mannheim, Germany), and insulin and PTH were 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 regarding 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 was completed.

Oral glucose tolerance test

A 75-g oral glucose tolerance test was performed according to WHO/ADA 2007 criteria [25]. The prevalence of normal glucose tolerance (NGT: 2-h 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: 2-h post load glucose between 7.8–11.1) as well as pre-diabetes (IFG/IGT) was determined. Plasma concentrations of glucose and insulin were measured at times −30, −15, 0, 30, 60, 90 and 120 min. According to Matsuda et al., an insulin sensitivity index (ISI composite) was calculated as 10 000/square root of [fasting glucose × fasting insulin] ÷ [mean glucose × mean insulin during OGTT]. This index is highly correlated with the rate of whole-body glucose disposal during a euglycemic insulin clamp in patients with varying degrees of glucose tolerance [26].

The area under the curve (AUC) for insulin and glucose during the OGTT was calculated using the trapezoid rule. These variables were implemented in the insulin secretion index; 

\[ \text{SeCF}_{AUC} = \frac{AUC_{Ins}}{AUC_{Glu}} \]

Pulse wave analysis and velocity

Pulse wave velocity of the carotid-femoral pulse wave was recorded sequentially at the carotid and femoral arteries using applanation tonometry (SphygmoCor®; AtCor Medical, Sydney, NSW, Australia) performed by the same observer (MH). Using simultaneous three-lead electrocardiogram recording of the R wave as the reference frame and calculating the time delay using a foot-of-the-wave method (intersecting tangent), the PWV was calculated by the system software. The distance between the carotid artery recording site and the sternal notch was subtracted from the distance from the sternal notch to the palpable femoral pulse. PWV was calculated as ratio between the distances travelled by the pulse wave and pulse transmis sion time.

The pulse wave was recorded from the radial artery of the right arm or, in the case of a fistula, from the contralateral arm with a high-fidelity micromanometer (SPC-301; Millar Instruments, Houston, TX, USA). A model of the central pressure waveform was synthesized by the SphygmoCor software using a validated transfer function as previously described [9]. The pulse wave analysis (PWA) was used to determine aortic augmentation as the difference between the second (caused by wave reflection) and the first systolic peak (caused by ventricular ejection). The augmentation index (AIX) serves as an integrated parameter for the cardiovascular function in the arteries and is calculated from the augmentation (\( \Delta P \)) and the central pulse pressure (PP) computed by the software from brachial systolic and diastolic pressure, (AIX = \( \Delta P/PP \times 100 \)). An average of two consecutive readings, each consisting of at least 20 sequentially recorded waveforms, was used for the analyses. AIX was adjusted for heart rate. Time to the foot of the reflected wave (Tr) was identified and represents the composite travel time of the pulse wave to the periph ery and its return. It is enhanced by increased pulse wave velocity and is a further index of conduit artery stiffness. Subendocardial variability ratio (SEVR) is the ratio of diastolic pressure time interval (ADP) /systolic pressure time interval (AS) [29] and was also determined. SEVR is associated with the pressure and time for coronary perfusion, and this has, in patients with known coronary artery disease, been found to indicate aggravating subendocardial ischaemia [30] due mainly to reduction in diastolic perfusion time. The reproducibility of PWA and PWV for two repeat scans of 10 uraemic patients from the present study was analysed using the Bland-Altman method. The mean (±SD) intra-observer difference was 0.1 ± 0.7 m/s for PWV, 1.7 ± 5.5% for AIX and −1.0 ± 8.8% for SEVR, which is in accordance with other groups [31,32].
Flow-mediated vasodilation and nitroglycerin-induced dilatation

An Acuson 128XP/10 MHz ultrasound system with extended frequency-imaging option and a 7-MHz linear transducer were used to measure the brachial artery dilatory responses to increased flow and to nitroglycerin (NTG) based on previous published methodology by our group and others [33,34].

FMD is dependent on the endothelial function [35], while nitroglycerin-induced dilatation (NID) is the maximal vasodilatory capacity independent of the endothelial function.

The ultrasound system was connected to a video recorder and to a computer equipped with a frame grabber and artificial neural network wall detection software (vessel image analysis (VIA)) developed by Sidhu et al. [33]. The VIA software automatically detects and tracks the anterior and posterior walls within a user-defined region of interest. Arterial diameter was measured by VIA at baseline (mean over 15 s) and continuously 5 min after release of a pneumatic tourniquet, which had been inflated for 4.5 min to a pressure of 300 mmHg distal to the segment of the artery being scanned. After 10 min of rest, 400 μg NTG (Nitroglycerin spray, Pohl-Boskamp, Hohenlockstedt, Germany) was administrated sublingually and arterial diameter again measured continuously for 10 min. FMD (defined as mean arterial diameter in percentage of baseline diameter over a 15-s period at 5 min after tourniquet deflation) was automatically calculated. NID was calculated similarly as mean arterial diameter in percentage of baseline diameter over a 15-s period at 55 s after tourniquet deflation) was automatically calculated. NID was calculated similarly as mean arterial diameter in percentage of baseline diameter over a 15-s period at 5 min after tourniquet administration.

Doppler-derived flow was measured at videotape using a pulsed-wave Doppler signal at a 70° angle to the vessel with the range gate (1.5 mm) in the centre of the artery at baseline (mean of four measurements) and at the maximum within the first 15 s after tourniquet release. Blood flow was calculated by multiplying the velocity time integral of the Doppler flow signal (corrected for angle) by the heart rate and the vessel cross-sectional area and percentage flow increase subsequently calculated.

External ultrasound measurements of FMD and NID have previously been shown to provide accurate and reproducible results [24,36] coefficients of variation of the diameter changes expressed as diameter in percentage of the baseline scan diameter (100%) in the present study was 4.4% and 4.1% for FMD and NID. This estimate was based on eight scans of the same subject from the present study population (within-patient variability). The measurements were performed on separate days within 2 weeks by the same investigator, and the variation was similar to previous reports [34,37].

Data regarding diagnosis of kidney disease, dialysis modality, duration of ESRD, antihypertensive treatment and previous myocardial infarction (MI) or apoplexia were obtained anamnestically from the medical record. Smoking history was obtained by questioning and given as ever smoking (present and previous) or not. Waist-hip ratio and weight and height were also measured.
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Glycaemic, inflammatory, endothelial and uraemic variables in 66 uraemic patients with and without pre-diabetes and 14 healthy controls

Table 2. Glycaemic, inflammatory, endothelial and uraemic variables in 66 uraemic patients with and without pre-diabetes and 14 healthy controls

<table>
<thead>
<tr>
<th></th>
<th>Normal glucose tolerance</th>
<th>Pre-diabetes</th>
<th>Healthy controls</th>
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<tbody>
<tr>
<td></td>
<td>Uraemic patients N = 39</td>
<td>N = 27</td>
<td>N = 14</td>
</tr>
<tr>
<td>Fasting p-glucose (mmol/L)</td>
<td>5.1 ± 0.4</td>
<td>5.2 ± 0.4</td>
<td>5.0 ± 0.3</td>
</tr>
<tr>
<td>HbA1C (%)</td>
<td>5.2 ± 0.3</td>
<td>5.3 ± 0.4</td>
<td>5.2 ± 0.2</td>
</tr>
<tr>
<td>p-glucose at 2 h (mmol/L)</td>
<td>6.7 ± 1.0</td>
<td>8.8 ± 1.6***</td>
<td>5.4 ± 1.1***</td>
</tr>
<tr>
<td>Insulin sensitivity index (ISI-composite)</td>
<td>7.3 ± 3.8</td>
<td>6.1 ± 3.3</td>
<td>14.7 ± 7.0***</td>
</tr>
<tr>
<td>AUC glucose (mmol/L/120 min)</td>
<td>7.7 ± 1.1</td>
<td>8.9 ± 1.2*</td>
<td>6.3 ± 1.2***</td>
</tr>
<tr>
<td>AUC insulin (mmol/L/120 min)</td>
<td>290 ± 189</td>
<td>262 ± 141</td>
<td>174 ± 107°</td>
</tr>
<tr>
<td>Insulin secretion index</td>
<td>38 ± 22</td>
<td>30 ± 17</td>
<td>17 ± 14</td>
</tr>
</tbody>
</table>

Inflammatory and endothelial

Von Willebrand factor antigen (kIU/L) | 1.8 ± 0.7 | 1.7 ± 0.6 | 0.96 ± 0.3***
C-reactive protein (mg/L) | 4 ± 3 | 5 ± 8 | 1 ± 1***
P-homocystein (µmol/L) | 25 ± 13 | 28 ± 13 | 14 ± 5***
P-urate (µmol/L) | 0.35 ± 0.1 | 0.33 ± 0.1 | 0.28 ± 0.1

Uraemic and lipids

P-creatinine (µmol/L) | 874 ± 305 | 889 ± 444 | 69 ± 9***
P-carbamid (µmol/L) | 20 ± 7 | 21 ± 9 | 4.7 ± 1.2***
P-haemoglobin (µmol/L) | 7.6 ± 1 | 7.4 ± 1 | 8.5 ± 1***
P-PTH (pmol/L) | 35 ± 32 | 24 ± 20 | 3.9 ± 1***
P-total cholesterol (mmol/L) | 4.7 ± 1.3 | 4.7 ± 1.3 | 4.1 ± 0.7***
S-LDL-cholesterol (mmol/L) | 3.0 ± 1.2 | 2.9 ± 1.1 | 2.4 ± 0.7***
S-HDL-cholesterol (mmol/L) | 1.4 ± 0.5 | 1.4 ± 0.5 | 1.7 ± 0.6
P-triglyceride (mmol/L) | 1.8 ± 1.2 | 1.7 ± 1.3 | 0.9 ± 0.56

Data are presented as mean ± SD, percent (%) or median with range. Wilcoxon rank sum test or unpaired t-test used where appropriate to test: Normal glucose tolerance patients vs. pre-diabetes patients; *P < 0.05, ***P < 0.0005. Uraemic patients vs. healthy controls; ¹P < 0.05, ²P < 0.005.

Results

Twenty-seven (41%) uraemic patients had pre-diabetes of which 25 had IGT and two IFG. The remaining 39 were normoglycaemic. Uraemic patients with pre-diabetes were comparable to normoglycaemic patients with regard to the causes of renal disease, modality of dialysis, duration of ESRD, smoking, blood pressure or antihypertensive medication (Table 1). Cardiovascular events [previous myocardial infarction (MI) or apoploxia] were registered in four (10%) of the normoglycaemic and two (7%) of the pre-diabetic uraemic patients compared to the patients with normal glucose tolerance (Figure 1). No difference in PWV in univariate analysis (data not shown). Type or number of antihypertensive drugs did not influence the PWV or AIX between haemodialysis and peritoneal dialysis patients were found (7.9 ± 3 m/s vs 8.8 ± 3 m/s and 26 ± 13 vs 23 ± 12, P = NS), but a significantly higher AIX was found in dialysis patients as compared to pre-diagnosis patients (15 ± 11 vs 24 ± 13, P = 0.01). PWV was significantly positively related to age (P < 0.0001), MAP (P = 0.005), baseline brachial artery diameter (P = 0.024), AUCglu120 min (P = 0.01) and pre-diabetes (P = 0.026) in a univariate analysis. Using multivariable analysis with pre-diabetes, age, sex, height, heart rate, MAP and dialysis status as variables, age (P < 0.0001) and MAP (P = 0.004) were independently related to PWV, and the model accounted for 53% of the variability in PWV (Table 4). Using AUCglu 120 or ISI instead of pre-diabetes did not result in any change in independent factors. Pulse wave analysis measured by augmentation index, Tr and SEVR revealed no difference between uraemic patients with and without pre-diabetes (Table 3). Augmentation index was positively associated to MAP (P = 0.04) and female sex (P = 0.001) and inversely associated to heart rate (P < 0.005) and height (P = 0.0004) in a univariate analysis. Using multivariable analysis with pre-diabetes, age, sex, height, heart rate and dialysis status as variables, age (P = 0.0004), female sex (P = 0.004), heart rate (P < 0.0001), height (P = 0.01), dialysis status (P = 0.01) and MAP (P = 0.002) were independently associated to augmentation index, and the model explained 63% of the variability in augmentation index (Table 4). Using AUCglu120 or ISI instead of pre-diabetes did not result in any change in independent factors.

The baseline brachial artery diameter did not improve the models, although it was associated with increased PWV in univariate analysis (data not shown). Type or number of antihypertensive drugs did not influence the
augmentation index or pulse wave results, and it was evenly distributed between groups (Table 1).

Flow-mediated vasodilatation

FMD, NID and the increase in brachial blood flow after ischaemia were impaired in uraemic patients as compared to healthy controls ($P < 0.005$, $P < 0.0005$ and $P < 0.05$). However, there was no difference in FMD, NID, baseline arterial diameter or increase in brachial flow between uraemic patients with and without pre-diabetes (Table 3). FMD was associated to height ($P = 0.04$) in univariate regression analysis, but with FMD or NID as the dependent variable in the multivariate analysis, no significant associations to independent variables were disclosed.

Inflammatory, endothelial and uraemic markers

Plasma homocystein, vWF, CRP, urate, PTH and serum lipids were higher in the uraemic patients compared to healthy controls.

Table 3. Arterial stiffness, endothelial and cardial function variables in 66 uraemic patients with and without pre-diabetes and 14 healthy controls

<table>
<thead>
<tr>
<th></th>
<th>Normal glucose tolerance</th>
<th>Pre-diabetes Uraemic patients</th>
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<tbody>
<tr>
<td></td>
<td>$N = 39$</td>
<td>$N = 27$</td>
<td>$N = 14$</td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Systolic (mmHg)</td>
<td>140 ± 21</td>
<td>144 ± 23</td>
<td>118 ± 10</td>
</tr>
<tr>
<td>Diastolic (mmHg)</td>
<td>84 ± 14</td>
<td>85 ± 10</td>
<td>73 ± 8</td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>56 ± 16</td>
<td>59 ± 17</td>
<td>45 ± 8</td>
</tr>
<tr>
<td>MAP</td>
<td>103 ± 15</td>
<td>104 ± 13</td>
<td>88 ± 8</td>
</tr>
<tr>
<td>Heart rate</td>
<td>70 ± 13</td>
<td>70 ± 10</td>
<td>61 ± 9</td>
</tr>
<tr>
<td>Arterial stiffness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic PWV (m/s)</td>
<td>7.3 ± 2</td>
<td>9.1 ± 3*</td>
<td>6.7 ± 1</td>
</tr>
<tr>
<td>SEVR (%)</td>
<td>155 ± 30</td>
<td>148 ± 29</td>
<td>191 ± 28</td>
</tr>
<tr>
<td>Augmentation index (%)</td>
<td>23 ± 13</td>
<td>25 ± 12</td>
<td>17 ± 16</td>
</tr>
<tr>
<td>Time to reflected wave, Tr (ms)</td>
<td>144 ± 11</td>
<td>145 ± 14</td>
<td>156 ± 14</td>
</tr>
<tr>
<td>Flow mediated vasodilatation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline diameter in brachial artery (mm)</td>
<td>4.3 ± 0.8</td>
<td>4.3 ± 0.9</td>
<td>3.8 ± 0.7</td>
</tr>
<tr>
<td>Flow mediated dilatation (% of baseline)</td>
<td>4 ± 5 (−1–19)</td>
<td>3 ± 4 (−6–12)</td>
<td>7 ± 3 (1–14)</td>
</tr>
<tr>
<td>Flow increase in brachial artery after ischaemia (% of baseline)</td>
<td>470 ± 200</td>
<td>480 ± 300</td>
<td>670 ± 300</td>
</tr>
<tr>
<td>Nitroglycerin-induced dilatation (% of baseline)</td>
<td>12 ± 6 (2–27)</td>
<td>12 ± 5 (3–23)</td>
<td>19 ± 5 (12–28)</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD and percent (%) or range. PWV: pulse wave velocity, SEVR: subendocardial variability ratio, Wilcoxon Rank Sum Test or unpaired $t$-test used where appropriate to test: Normal Glucose Tolerance patients vs. Pre-diabetes patients; *$P < 0.05$. Uraemic patients vs. Healthy controls; §$P < 0.05$, §§$P < 0.005$, §§§$P < 0.0005$. 

Fig. 1. Pulse wave velocity in 66 uraemic patients with and without pre-diabetes and 14 healthy controls.
controls (Table 2), but no difference between pre-diabetic and normoglycaemic uraemic patients was demonstrated.

Discussion

The main findings in this study were a high prevalence (41%) of pre-diabetes among non-diabetic ESRD patients on the waiting list for transplantation combined with findings, suggesting that increased aorta stiffness is more prevalent in pre-diabetic uraemic patients as compared to uraemic patients with a normal glucose tolerance test.

The two uraemic groups were comparable regarding age, time on dialysis and other key clinical and demographic parameters except for gender. Female sex was more prevalent in the pre-diabetic group. This skewed distribution is, however, in keeping with the higher prevalence of females seen in population-based studies of pre-diabetes [38], and the sex distribution in the uraemic patients without pre-diabetes was similar to what is seen in the total population of patients with ESRD in Denmark [39]. Non-participation was mainly due to practical issues such as long distance to the hospital and therefore does not seem to bias our results. All tests had been made under standardized conditions. In particular, the influence of dialysis status had been minimized because all investigations took place in the first days after hemodialysis, and in patients treated with peritoneal dialysis, the peritoneal cavity had been drained at 6 a.m. on the day of examination. The glucometabolic status was measured using the golden standard of a glucose tolerance test with simultaneous measurements of p-insulin.

The reference range of aortic PWV in normal subjects similar of age to our cohort is often reported to be below 6–8m/s [18,40], and the presence of hypertension and ESRD is associated with increased cardiovascular disease and all-cause mortality [11,41]. A level of 9m/s as seen in these uraemic patients with pre-diabetes may reflect an advanced stage of vascular disease in the arterial wall. It is well known that the carotid-femoral PWV measured by different methods is increased in patients with isolated pre-diabetes and diabetes [42]. It is, however, a new observation that an increased carotid-femoral PWV in uraemic patients may be related to pre-diabetes. Using univariate analysis, both AUC Glu120 min and presence of pre-diabetes was associated to PWV in uraemic patients, but the multivariate analysis only disclosed age and blood pressure as independent determinants of PWV. When analysing the three subgroups separately, we found that in the uraemic patients with NGT and pre-diabetes as well as in healthy controls, PWV was positively and independently associated to age and MAP. In healthy controls, the 2-h glucose was also positively ($r = 0.78, P = 0.03$) associated to PWV. Based on these observations, it could be speculated if the higher levels of blood pressure in uraemic patients may have masked a possible effect of higher glucose levels on PWV. This may find support in the observation that presence of pre-diabetes and AUC Glu120 min was related to PWV in uraemic patients using the univariate analysis ($P < 0.01$). Furthermore, the association between pre-diabetes and PWV reached a $P$ level of 0.11 in the multivariate analysis. We may therefore have overlooked significant associations due to the relatively small number studied.

The levels of AIX, SEVR and Tr were similar in uraemic patients with and without pre-diabetes and show that other factors are responsible for the vascular pathophysiology in uraemia and the demonstrated differences in these parameters in uraemic patients as compared to healthy controls. Indeed, we found associations between increased blood pressure, heart rate and age on both PWV and AIX, which are in keeping with others [43], and indicate that these parameters are important determinants of arterial stiffness also in uraemic patients.

In addition, dialysis treatment was also independently associated to a higher AIX, indicating that the severity of ESRD or the dialysis per se deteriorates arterial function [44].

The endothelial function in uraemia was significantly reduced as indicated by an overall lowered FMD and in-
creased von Willebrand factor antigen concentration in uraemic patients. However, a further reduction of endothelial function in the uraemic patients with pre-diabetes was not noted, suggesting that the uraemic state has a more pronounced impact on the endothelial dysfunction than presence of pre-diabetes.

PWV was positively associated to the diameter of the brachial artery in the uraemic patients, but no other associations between measures of arterial stiffness and endothelial dysfunction were detected in this population.

Several measures of the metabolic syndrome such as waist–hip ratio, plasma triglycerides and blood pressure were increased in the uraemic patients, but no further increment was noted with presence of pre-diabetes. This is in accordance with a remarkable reduction in insulin sensitivity in the uraemic patients with only a tendency to further reduction in the patients with pre-diabetes. The patients with pre-diabetes had for the majority increased postprandial glucose increment, and this could be due to an impaired incretin effect as it is known that patients with type 2 diabetes and subjects with impaired glucose tolerance have reduced postprandial GLP-1 secretion [45,46]. Ureaemia per se could have a deleterious effect on the GLP-1 secretion, which is presently studied further in our laboratory. HbA1C was not significantly elevated in our group of patients with pre-diabetes. This might reflect that only a small deterioration in the glucose metabolism was seen or may be due to the fact that a certain level of glucose is often reflected by a lower HbA1C level in uraemic patients than in healthy controls.

Finally, height was inversely associated to AIX as previously shown [47].

Based on our discussion above and the participation rate of 48% in this population of chronic diseased patients, it is likely that our findings can be generalized to all uraemic patients accepted for kidney transplantation. Consequently, the findings of our study suggest that increased PWV noted in new onset diabetes after kidney transplantation [48,49] may already, at least in part, be present before the transplantation and a result of pre-diabetes or insulin resistance in the uraemic patients awaiting a kidney transplant.

In conclusion, a high prevalence of pre-diabetes, impaired insulin resistance, increased arterial stiffness of aorta as well as impaired augmentation index and vasodilatation was demonstrated in uraemic patients prior to kidney transplantation. Increased arterial stiffness of aorta and augmentation index were independently associated with age and blood pressure. This supports the implementation and continuation of interventions aiming to reduce the cardiovascular load of risk factors including new onset diabetes mellitus prior to kidney transplantation in uraemic patients.

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Outcome of atrial fibrillation among patients with end-stage renal disease

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Abstract

Background. End-stage renal disease (ESRD) patients are more at risk for atrial fibrillation (AF) than the general population. However, the prognosis in ESRD patients with paroxysmal AF (PaAF), permanent AF (PAF) and paroxysmal AF transformed to permanent AF (TAF) is unknown.

Methods. In this retrospective longitudinal study, all ESRD patients with PaAF, PAF and TAF between January 2001 and December 2007 were reviewed. The develop-