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ORIGINAL ARTICLE

Diabetes mellitus and renal failure: effects on large artery stiffness

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Diabetes mellitus and end-stage renal disease are two pathologic entities associated with increased cardiovascular risk. Several studies have shown that arterial stiffness is increased in both cases and contributes to the increased risk. In order to determine the effect of diabetes and renal failure on arterial stiffness, we conducted a case-control study. One hundred and twenty-two diabetic patients were compared to 122 non-diabetic patients matched to the study group for sex, age, mean arterial pressure, number and localisation of the atherosclerotic alterations. Arterial stiffness was assessed by automatic measurement of the aortic pulse wave velocity (PWV) and by measuring the peripheral and carotid pulse pressure (PP) and reflected waves through analysis of the pulse wave using the principle of applanation tonometry. Aortic PWV was significantly higher in the diabetic subgroup as well as PP at the peripheral and central levels for the same age and mean arterial pressure. In addition, renal failure was independently associated with an increased aortic PWV but not PP in the general population. Independent of the degree of renal failure, a fall in the glomerular filtration rate was also associated with increased aortic PWV. No interaction was noted between renal failure and diabetes mellitus. In conclusion, this study shows that diabetic patients have higher arterial stiffness compared to non-diabetic ones having one or more cardiovascular risk factors, manifested by increased aortic PWV and PP. In addition, renal failure, irrespective of its degree and independent of diabetes mellitus, is associated with increased aortic PWV but not PP.
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Introduction

The arterial system is a multifunctional organ, ensuring adequate blood supply to body tissues, smoothing out the pressure oscillations resulting from intermittent ventricular ejection and having an endocrine, a paracrine and an autocrine function. In addition, it propagates pressure and flow waves at a certain velocity which is largely determined by the elastic properties of the arterial wall.[1]

Several physiologic situations such as aging[2] and menopause[3] and pathologic entities like hypertension (HTN),[4] diabetes mellitus (DM),[5] atherosclerosis,[6] and end-stage renal disease (ESRD)[7] are associated with and/or contribute to increased arterial stiffness. Consequently, the pulse wave velocity (PWV), ie the velocity of the pulse wave to travel a given distance between two sites of the arterial system, increases. As a result, the pulsatile blood pressure (BP) increases, thereby causing increased left ventricular afterload and altered coronary perfusion.[4,8] High systolic blood pressure (SBP) and pulse pressure (PP), low diastolic blood pressure (DBP), and left ventricular hypertrophy (LVH) have been identified as independent factors of cardiovascular (CV) morbidity and mortality in the general population.[9–12] In addition, increased arterial stiffness, evaluated by the noninvasive measurement of the PWV, constitutes an independent CV risk factor in the hypertensive population.[8]

DM is a well known pathologic entity associated with an increased vascular risk related to both micro-angiopathy and macro-angiopathy.[13–15] Large scale interventional trials, mainly the Diabetes Control and Complications Trial (DCCT)[16] for type I DM and the United Kingdom Prospective Diabetes Study (UKPDS)[17] for type II DM, have demonstrated that tight blood glucose control is essential for the prevention of micro-vascular disease. However, macrovascular events contribute the most to the increased morbidity and mortality in the type II diabetic population, hence the importance of preventing the occurrence of such events.[17] The UKPDS has demonstrated that antihypertensive therapy, through either a direct effect (on the vascular wall) or an indirect one (by lowering BP), constitutes the cornerstone for the prevention of macroangiopathy.[17]

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Several studies have shown that large arterial stiffness, which frequently precedes macro-vascular events, is increased in diabetic patients and contributes to the increased morbidity and mortality in that population.[5,18–22]

Advanced uraemia, on the other hand, is associated with structural remodelling of the arterial system characterised by dilatation and hypertrophy of the wall of large arteries. These changes are similar to those observed with aging but are more pronounced in uraemic than in non-uraemic patients for the same age.[23–25] In addition, Blacher *et al*[26] have demonstrated that aortic PWV is significantly and independently associated with an increase in all-cause and CV mortality in haemodialysed patients. However, whether arterial rigidity is increased early in the course of renal failure is unknown.

The goal of the present study was: (1) to compare aortic PWV and central PP and reflection waves of diabetic patients with those of non-diabetic patients having one or more CV risk factor, (2) to test the effect of renal failure on the above-mentioned haemodynamic parameters, and (3) to look for a possible interaction between the two CV risk factors: DM and renal failure.

Methods

Patients

Between January 1996 and June 1997, 1500 patients aged 15 to 91 years, were admitted to the department of Internal Medicine and Hypertension at Broussais Hospital, Paris, France, for CV evaluation ordered by their general practitioner or cardiologist owing to the presence of one or more CV risk factors including high BP, smoking, dyslipidaemia, DM, and/or family history of premature CV disease, with or without previously identified atherosclerotic alterations (AA). Of these, diabetic subjects were selected according to the following criteria: a fasting plasma glucose of more than 7 mmol/L or the presence of anti-diabetic medication (sulfonylurea, biguanide and/or insulin). The study group therefore included 122 diabetic subjects (81 men, 41 women) with a mean age (±s.d.) of 58.3 ± 10 years. Forty patients (32.7%) were taking at least one anti-diabetic medication upon inclusion and 112 (92%) had HTN, of whom four were never treated. The diagnosis of HTN was considered when SBP was >140 mm Hg and/or DBP >90 mm Hg, measured by sphygmomanometry, in the supine position, with a minimum of three casual measurements during the last month, or when antihypertensive therapy was present. The antihypertensive drugs included calcium channel blockers (CCB) (67 patients), beta-blockers (BB) (39 patients), diuretics (38 patients), central acting agents (18 patients), angiotensin-converting enzyme inhibitors (ACEI) (37 patients), angiotensin II antagonists (AIIA) (five patients), and alpha-blockers (AB) (five patients), either alone or in combination. Twenty-four diabetic patients (19.7%) were treated for dyslipidaemia (statins and/or fibrates). Dyslipidaemia was defined as a total/high-density lipoprotein (HDL) cholesterol ratio >5 or the presence of a hypocholesterolaemic drug (statin and/or fibrate). AA was considered whenever clinical events at the coronary, cerebral, aortic or peripheral levels occurred and on the basis of radiologic tests performed during hospitalisation. For a description of AA, the usual criteria were used according to the International Classification of Diseases (9th revision) for coronary heart disease, cerebrovascular disease, peripheral vascular disease, and abdominal aortic aneurysm. According to the above definition, AA was noted in 12 diabetic patients (9.8%) involving one or more vascular sites. The mean number of vascular sites involved by AA in the diabetic population was 1.08 ± 0.3 per patient. The extent of atherosclerosis was assessed as the number of vascular sites involved by AA: 0 (110 patients), 1 (11 patients) or 2 (one patient).

The control group (non-diabetic) was selected from the same population and matched to the study group for sex, age, calculated mean arterial pressure (MAP) (see below), number and localisation of the AA. It consisted of 122 subjects (81 men, 41 women) with a mean age (±s.d.) of 58.1 ± 10 years. A total of 110 patients (90.2%) were hypertensive of whom eight were never treated. The antihypertensive medications included CCB (48 patients), BB (42 patients), diuretics (33 patients), central acting agents (16 patients), ACEI (36 patients), AIIA (two patients), and AB (four patients), either alone or in combination. Thirteen patients (10.6%) were treated for dyslipidaemia and 12 (9.8%) had AA involving one or more vascular sites with a mean number of 1.08 ± 0.3 sites per patient. A total of 110 patients had no AA, 11 patients had one atherosclerotic site and one patient had two atherosclerotic sites.

Each subject provided informed consent for the study, which was approved by our institutional review board. A questionnaire was filled out at inclusion for each patient and contained information concerning age, sex, weight, height, body mass index, family (first-degree relatives) history of premature CV events (<55 years in men and <60 years in women), personal history of DM, dyslipidaemia, smoking habits, previous diseases, and use of medications including antihypertensive drugs.

Methods

The measurements were performed in the morning after an overnight fast, each patient being in the supine position. Brachial BP was measured with a mercury sphygmomanometer after 15 minutes of rest. Phases I and V of the Korotkoff sounds were considered as SBP and DBP respectively. The MAP was calculated from the following formula:

MAP = DBP + (SBP – DBP)/3. Five measurements 2 min apart were averaged.

After BP determination the PWV was measured in a controlled environment at 22°C using an automatic device: the 'Complior' (Colson, Paris, France). This method allows an online pulse wave recording and automatic calculation of the PWV using two transducers, one placed at the base of the neck for the common carotid artery and the other over the femoral artery, as previously described.[1] The validation of this method and its reproducibility have been previously described, with an intra-observer and an inter-observer repeatability coefficients of 0.935 and 0.890 respectively.[27] Under similar conditions and for local pressure wave determinations, brachial and radial artery systolic, diastolic and mean pressures were considered equivalent, taking into account the small degree of pressure wave amplification between the two sites. Radial and carotid pressure waves were then measured directly by applanation tonometry using a Millar transducer.[28] After planimetry of the radial and carotid pressure curves, calibration was performed as previously described[28] assuming that MAP and DBP were identical at the two arterial sites. The augmentation index, defined as the percent difference between the second and the first systolic peaks of the BP curve, was then measured from the carotid curve according to standard procedures[28] and used as an index of central wave reflections. Reproducibility of the method has been published in detail elsewhere.[29]

Heart period was determined from the three-lead orthogonal ECG. On the basis of the 8-s recording, the average heart rate was calculated (in beats per minute) during that period. ECG left ventricular hypertrophy was defined as a Sokolow index superior to 35 mm. Waist circumference midway between the lowest rib and the iliac crest, and hip circumference at the level of the great trochanters were measured with a flexible tape. Venous blood samples were obtained after an overnight fast. Plasma was separated without delay at 4°C in a refrigerated centrifuge and stored at 4°C (for determination of routine chemistry profile by standard methods) until analysis. Total cholesterol and triglycerides were measured in the plasma via an enzymatic reaction using a bioMerieux reagent (Olympus 560), and (HDL) cholesterol was measured in the supernatant after precipitation of apolipoprotein B-containing lipoproteins with phosphotungstic acid and magnesium ions (Olympus AU 560). Low-density lipoprotein (LDL) cholesterol was calculated from the formula of Friedewald for patients with serum triglyceride concentrations <4.0 mmol/L. Serum and urinary creatinine was measured using the kinetic method of 'Jaffé' and the urinary proteins quantitated by a colorimetric method (Olympus AU 560).

The formula of Cockcroft–Gault was used for the estimation of the glomerular filtration rate (GFR) and was adjusted for sex (*0.85 for females). The values were expressed in ml/mn/1.73 m^2. Renal failure was considered for a GFR $\leqslant$80 ml/mn/1.73 m^2. A total of 132 patients (54%) had renal failure according to the above definition, of which 19 had a GFR below 50 ml/mn/1.73 m^2. When 24-h urine collection was considered, only 50 patients had adequate collection (according to normal values of daily creatinine excretion adjusted for age and sex). In these patients other urinary parameters were measured including electrolytes, proteinuria and when necessary, microalbuminuria. The GFR was also estimated in this subgroup from the creatinine clearance and from the equation proposed by the Modification of Diet in Renal Disease (MDRD) group.[30] The three methods estimating the GFR were compared, each two apart, using the linear regression and Bland–Altman plots. The best correlation ($r = 0.89$) and agreement were noted between the formula of Cockcroft–Gault and that of the MDRD group. This result is similar to the MDRD group's when the three methods were considered.

Analysis

Statistical analysis was performed on NCSS 6.0.21 software.[31] Student's *t*-test was used for comparison of normally distributed continuous variables between the two subgroups (diabetic and non-diabetic). DM and renal failure, as well as some other parameters, were used as dummy variables (eg, 1 = diabetic patient; 0 = non-diabetic patient). All testing was double-sided. A value of $P \leqslant 0.05$ was considered significant. The analysis of variance (ANOVA) was used to determine the effect of diabetes and of renal failure on the PWV and to look for any possible interaction between these two parameters.

Simple regression was performed to evaluate linear associations between the haemodynamic parameters, specifically the PWV and the PP, and the other biologic, morphologic and therapeutic variables. All the parameters showing significant correlation with the PWV and/or the PP were integrated in a multiple regression analysis to determine the ones independently associated with a significant modification of the above parameters. This analysis was performed in the general population (for the PWV and the PP) and in the two subgroups (for the PWV).

Results

Comparison of means between the two subgroups

Table 1 shows the anthropometric characteristics of the diabetic and the non-diabetic patients. Independent of age and sex, the body weight, body mass index (weight (kg)/(height (m))^2), waist circumference and waist/hip ratio were significantly higher in the diabetic subgroup.

The haemodynamic parameters are presented in

Table 1 Anthropometric characteristics of patients in the two subgroups

	Diabetic patients (n = 122)	*Non-diabetic patients (n = 122)*	*P*
Age (years)	58.3 ± 10	58 ± 10	NS
Gender M (%)	81 (66%)	81 (66%)	NS
F (%)	41 (34%)	41 (34%)	NS
Weight (kg)	83.6 ± 14.4	76.5 ± 12.5	<0.0001
Height (cm)	168 ± 0.09	168 ± 8	NS
BMI (kg/m^2)	29.3 ± 4.4	26.9 ± 4	<0.0001
Waist circumference (cm)	102 ± 11	96 ± 11	=0.0004
Waist/hip ratio	0.97 ± 0.07	0.94 ± 6.6	=0.014

Values are expressed as means ± s.d. except for gender which is represented by the number and the percentage of patients. M, male; F, female; NS, nonsignificant; BMI, body mass index.

Table 2. Systolic, diastolic and mean brachial BP values were comparable between the two subgroups. However, brachial PP, as well as radial and carotid were significantly higher in the diabetic subgroup ($P = 0.009$; $P = 0.0015$ and $P = 0.011$ respectively). In addition, aortic PWV was also significantly higher in the diabetic subgroup (13.8 *vs* 12.3 m/s, $P = 0.0017$). However, reflected waves, as assessed by the carotid augmentation index, were comparable between the two subgroups.

Table 3 shows the CV risk factors of the two subgroups. The lipid profile is significantly altered in the diabetic patients with a low HDL-cholesterol, high total cholesterol/HDL ratio and high serum triglyceride concentration. On the other hand, smoking habits, AA and GFR values were comparable between the two subgroups.

Table 2 Haemodynamic parameters of diabetic and non-diabetic subjects

	Diabetic patients (n = 122)	*Non-diabetic patients (n = 122)*	*P*
SBP brachial (mm Hg)	148.7 ± 19	144.8 ± 17.5	NS
DBP brachial (mm Hg)	82.6 ± 12	84 ± 11	NS
MAP brachial (mm Hg)	104 ± 12	104 ± 11.7	NS
PP brachial (mm Hg)	66 ± 18.5	60.6 ± 14	=0.009
HR (bpm)	68 ± 11.2	66 ± 9.7	NS
PWV (m/s)	13.4 ± 2.8	12.3 ± 2.6	=0.0017
PP radial (mm Hg)	65.6 ± 18	57 ± 13	=0.0015
PP carotid (mm Hg)	53.4 ± 16.6	47 ± 13	=0.011
Augmentation index carotid (%)	121 ± 22.5	120 ± 22	NS
PP aortic (mm Hg)	50.5 ± 16.6	45 ± 14.1	=0.03

Values are expressed as means ± sd. SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; HR, heart rate; bpm, beats par minute; PWV, pulse wave velocity; NS, nonsignificant.

Table 3 Cardiovascular risk factors in diabetic and non-diabetic patients

	Diabetic patients (n = 122)	*Non-diabetic patients (n = 122)*	*P*
HTN	112 (92%)	110 (90%)	NS
Total cholesterol (mmol/l)	5.4 ± 1	5.6 ± 1	NS
HDL cholesterol (mmol/l)	1.2 ± 0.37	1.4 ± 0.42	=0.0008
Total chol/HDL	4.7 ± 1.4	4.3 ± 1.3	=0.018
Triglycerides (mmol/l)	1.6 ± 1	1.2 ± 0.6	<0.0003
Smoking (packs/year)	13.7 ± 21	12.6 ± 18	NS
AA	12 (10%)	12 (10%)	NS
Number of atherosclerotic sites/patient	1.08 ± 0.3	1.08 ± 0.3	NS
Fasting blood glucose (mmol/l)	8.5 ± 2.7	5.7 ± 0.6	<0.0001
Pcr (μmol/l)	89.4 ± 23.2	88.2 ± 20.4	NS
GFRC-G (ml/mn/1.73m^3)	81 ± 24	77 ± 22	NS

Values are expressed as means ± s.d. except for hypertension and atherosclerotic alterations which are represented by the number and the percentage of patients. HTN, hypertension; Total chol, total cholesterol; Smoking; tobacco consumption expressed in packs per year; AA, atherosclerotic alterations; Pcr, plasma creatinine concentration; GFRC-G, glomerular filtration rate estimated by Cockcroft–Gault formula; NS, nonsignificant.

The medications taken by the patients at inclusion are presented in Table 4. More patients in the diabetic subgroup were taking CCB, aspirin and hypolipaemic drugs compared to non-diabetic patients ($P = 0.007$, $P = 0.014$ and $P = 0.05$ respectively).

Analysis of variance

Results of the ANOVA are presented in Table 5. DM and renal failure were independently associated

Table 4 Medications taken by the patients at inclusion

	Diabetic patients (n = 122)	*Non-diabetic patients (n = 122)*	*P*
Diuretics	38 (31%)	33 (27%)	NS
ACEI	37 (30.3%)	36 (29.5%)	NS
Beta-blockers	39 (32%)	42 (34.4%)	NS
Central acting drugs	18 (15%)	16 (13%)	NS
Alpha-blockers	5 (4%)	4 (3.3%)	NS
AIIA	5 (4%)	2 (1.6%)	NS
CCB	67 (55%)	48 (39.3%)	0.007
Aspirin	23 (19%)	10 (8.2%)	0.014
Hypolipaemic drugs	24 (19.7%)	13 (10.6%)	0.05

Values correspond to the numbers and the percentages of patients, ACEI, angiotensin-converting enzyme inhibitors; AIIA, angiotensin II receptor antagonists; CCB, calcium channel blockers; NS, nonsignificant.

Table 5 Effect of DM and renal failure on aortic PWV (ANOVA)

	DM = 0 RF = 0	*DM = 1 RF = 0*	*DM = 0 RF = 1*	*DM = 1 RF = 1*	*Effect of DM*	*Effect of RF*	*Interaction*
PWV (m/s)	11.4	12.8	12.9	13.9	+	+	–

DM, diabetes mellitus; RF, renal failure; 0, absence of the disease; 1, presence of the disease; PWV, pulse wave velocity.

with an increase in aortic PWV ($P = 0.0003$ and $P = 0.0002$ respectively). No interaction was noted between the two parameters. As far as PP, only DM was associated with a significant increase of this haemodynamic parameter at the radial and carotid levels. Again, no interaction between DM and renal failure was noted.

Multiple regression analysis

Multiple regression analysis has shown that age, MAP, fasting blood glucose level, tobacco consumption and GFR (estimated from the Cockcroft–Gault formula) were independently associated with increased aortic PWV in the general population (Table 6). The relative contribution of each parameter was 18.5% ($P < 0.0001$) for age, 10% ($P < 0.0001$) for MAP, 3.8% ($P = 0.0003$) for fasting blood glucose level, 1.3% ($P = 0.02$) for smoking and 0.4% ($P = 0.05$) for GFR. In the diabetic subgroup, only age and MAP were independently associated with increased PWV (23% and 8% variance respectively) while in the non-diabetic subgroup age, MAP, fasting blood glucose and GFR were associated with increased aortic PWV (15.7%, 12.5%, 1.5% and 2.3% variance respectively) (data not shown).

As far as carotid PP, age, MAP, DM and smoking, but not GFR, were independently associated with a significant increase in the general population (data not shown).

Table 6 Variables independently associated with an increase in PWV in the general population

	β	*Standard error of β*	*P*	*Contribution to the modification*
Age	0.11	1.74	<0.0001	18.5%
MAP	6.67	1.26	<0.0001	10%
Fasting blood glucose	0.22	6.09	0.0003	3.8%
Smoking	0.01	7.47	0.02	1.3%
GFR	–1.45	7.51	0.05	0.4%

β, regression coefficient; MAP, mean arterial pressure; smoking, tobacco consumption expressed in packs-year; GFR, glomerular filtration rate estimated by the formula of Cockcroft–Gault and expressed in ml/min/1.73 m^2

Discussion

The salient findings of this study were that in a population of patients having one or more CV risk factors, aortic PWV and central PP are significantly and independently higher in diabetic compared to non-diabetic subjects. Similarly, for the same age and level of MAP, renal failure, defined as an estimated GFR of $\leqslant$80 ml/min/1.73 m^2, is associated with increased PWV without interaction with DM. In addition, age, MAP, fasting blood glucose level, smoking and GFR are independently associated with increased PWV in the general population.

In the present study, we used PWV, which is a marker of aortic stiffness, since it is related to the square root of the elasticity modulus and to the thickness/radius ratio.[4] The PWV, determined from foot-to-foot transit time in the aorta, offers a simple, reproducible, and noninvasive evaluation of regional aortic stiffness. This noninvasive superficial measurement allows only an estimate of the distance travelled by the pulse, and accurate measurements of this distance are obtained only with invasive procedures. In this regard, some authors suggested a possible correction based on anatomic dimensions of the body,[32] whereas others recommended subtracting the distance between the suprasternal notch and the carotid location from the total distance when the carotid pulse is recorded instead of the aortic arch pulse, because the pulse wave travels in the opposite direction at that level.[4] In fact, because arteries become longer and tortuous with age, the path lengths determined from superficial linear measurements are underestimated. Repeatability studies, checks made with Bland–Altman diagrams, and modern computer technology made it quite feasible to simply investigate aortic stiffness in CV epidemiological studies. Since the principal factors modulating the level of PWV are age and BP[2,4] studies using PWV should adjust the values obtained to these two parameters.

For local PP determinations, brachial and radial artery systolic, diastolic, and mean pressures were considered equivalent, taking into account the small degree of pressure wave amplification between these sites. Thoracic aortic pressure waves were derived from the radial artery pressure wave using a Millar transducer. Separately, ascending aortic pressure waves were synthesised from the carotid waves determined by tonometry. There was close agreement between the contour of the aortic pressure waves synthesised from the two sites. At each site, PP was averaged for a series of waves over a 10-s period. The repeatability coefficients after 1-and 3-month intervals were 6.8 and 7.2 mm Hg, respectively.[23,33,34] As expected, carotid PP was lower than radial PP but both PP were significantly higher in diabetic than in non-diabetic subjects.

Pulse wave velocity, pulse pressure and diabetes

In the present study, aortic PWV and PP were significantly higher in diabetic patients compared to non-diabetic patients whereas the reflected waves, as assessed by the augmentation index, was comparable between the two subgroups. This finding indicates that the observed results are due mainly to functional and/or structural alterations of the large artery wall.

DM is associated with an increased vascular risk related not only micro-angiopathy but also to macro-angiopathy.[13–15] The prevention of micro-angiopathy, ie retinopathy and nephropathy, requires tight blood glucose control.[16] On the other hand, the role of hyperglycaemia in the pathophysiology of macro-angiopathy remains controversial and the prevention of macro-vascular events seems to involve the treatment of CV risk factors associated with DM, essentially HTN.[17] Several studies[35–41] have analysed the effect of DM on the arterial wall in an attempt to determine early indices of diabetic alteration. The results are heterogeneous but there is a general tendency toward an increase of the arterial stiffness in diabetic and in insulin resistant patients.[35–41] DM affects the arterial wall by altering its metabolic environment and its structure. These alterations may be due either to the lack of insulin effect at the molecular level, or to the direct or indirect consequences of this defect, ie hyperglycaemia. Our results have shown that in a population of patients having one or more CV risk factors, age, MAP, fasting blood sugar, smoking and GFR (assessed from the Cockcroft–Gault formula) are independently associated with increased aortic PWV. On the other hand, only age and MAP are independently associated with increased stiffness in the diabetic subgroup. This observation raises the possibility that fasting blood sugar is probably not directly implicated in the pathophysiology of increased arterial stiffness and suggests that factors such as those resulting from the formation of advanced glycosylation end-products[42] may be involved.

Pulse wave velocity, pulse pressure and renal failure

Advanced renal failure is associated with structural remodelling of the arterial wall characterised by dilatation and hypertrophy.[23] Intima-media thickness increases and the elastic properties of the arterial wall become altered leading to increased PWV and to early return of reflected waves.[7,23,43,44] The structural alterations have been reported in experimental uraemia[45] and in arteries of uraemic patients.[46] Although patients with ESRD have increased risk of accelerated atherosclerosis,[47,48] the described changes of the arterial wall are independent of this parameter since they have been shown to be present at the level of the radial artery, where atherosclerosis is practically absent.[44,49] Recently, Blacher *et al*[26] have demonstrated that increased aortic PWV is an independent risk factor of all-cause and CV mortality in haemodialysed patients, a finding recently confirmed by therapeutic trial.[50]

All these previous studies have been conducted in patients with advanced uraemia. However, the level of the GFR below which the arterial changes start to be noticed has not been established yet. Our results have shown that renal failure, defined as an estimated GFR $\leqslant 80$ ml/min/1.73 m^2, is independently associated with increased aortic PWV in a population of patients having one or more CV risk factors. In addition, the GFR is negatively correlated to the PWV in the same population, whereas no correlation was found between renal failure or the GFR and the PP. Thus, our study is one of the first to show that whatever the degree of renal failure, a fall in the GFR is associated with an increase of aortic stiffness. In addition, independent of the classical risk factors accompanying uraemia, like HTN and dyslipidaemia, and which may potentially contribute to the increased arterial stiffness, renal failure is associated with increased aortic PWV. This result which had no interactions with the findings related to DM could be related to the metabolic alterations encountered in renal failure.[43]

In conclusion, irrespective of age and MAP, DM and renal failure are independently associated with increased stiffness of the large arteries, in a population of patients having one or more CV risk factors. DM is also associated with increased PP, probably as the consequence of increased PWV. Thus structural and functional alterations of the arterial wall may represent a therapeutic target for the prevention of macro-vascular events in DM. Irrespective of the degree of renal failure, a drop in the GFR is independently associated with increased aortic stiffness. This functional disturbance is probably related to the metabolic alterations observed in uremic patients.

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