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Microvascular Complications and their Association with Survival over Five years in the GERODIAB Cohort of Elderly French Type 2 Diabetic Patients

Jean-Pierre Le Floch[1*], Jean Doucet[2], Christiane Verny[3], Bernard Bauduceau[4]

[1]Department of Diabetology and Endocrinology, Villecresnes Medical Hospital, Villecresnes, France

[2]Department of Internal Medicine, Geriatrics and Therapeutics, Saint Julien Hospital, Rouen University Hospital, Rouen, France

[3]Department of Gerontology, Bicêtre University Hospital, France

[4]Department of Endocrinology, Begin Hospital, Saint Mandé, France

[*]**Corresponding author:** Jean-Pierre Le Floch, Department of Diabetology and Endocrinology, Villecresnes Medical Hospital, 8 boulevard Richerand, 94440 Villecresnes, France. Tel: +33145955757; Fax: +33145697584; Email: jplefloch@dietvill.com

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Abstract

Introduction: The relationship between microvascular complications of diabetes and mortality remains uncertain. The GERODIAB study is a multicentre prospective observational study performed over five years in French type 2 diabetic patients aged 70 years or above. This report deals with microvascular complications and their relationship with survival.

Methods: Consecutive ambulatory patients (n=987; median age=77 years [IQR=73–80]) were included from 56 diabetic centres over one year. Individual characteristics, history and complications of diabetes, geriatric factors, and clinical and biological parameters were recorded. Survival was analysed using the Kaplan-Meier method and proportional hazards multivariate regression models.

Results: The frequency of microvascular complications increased from baseline to five years: retinopathy 25 to 28%, macular oedema 3 to 9%, MDRD <60mL/min 31 to 52%, MDRD <30mL/min 3 to 9%, peripheral neuropathy 28 to 48%. Nephropathy (P<0.0001) and neuropathy (P=0.0003) were strongly associated with mortality, whereas retinopathy (P=0.57) and macular oedema (P=0.56) were not. In a multivariate model, among all the microvascular complications, nephropathy was the only one included (HR=1.84, CI=1.26-2.07, chi²=9.21, P=0.0013). When considering all the degenerative complications of diabetes, heart failure was the strongest predictor of mortality (HR=1.96, CI=1.45-2.64, chi²=19.49, P<0.0001).

Conclusions: Nephropathy and peripheral neuropathy were associated with poor survival in elderly type 2 diabetic patients, with nephropathy being the strongest predictor of mortality. Nephropathy was strongly associated with heart failure, which predicted mortality more accurately.

Keywords: Elderly; Nephropathy; Neuropathy; Other Complications; Retinopathy

Introduction

In Western countries, approximately one-quarter of the people are over 65 years of age are diabetic, and more than one-third of the diabetic patients are 70 years or older [1-2]. The well-known microvascular complications of diabetes and their relationship with glucose control have been largely studied in younger diabetic patients [3-6]. However, their relationship with mortality should be studied in elderly populations because the degenerative consequences of diabetes and aging accumulate in the elderly [7,8]. Such studies have not commonly been performed in large populations of elderly diabetic patients.

The GERODIAB study is a multi-centre, prospective, observational study that aims to describe mortality in French type 2 diabetic patients aged 70 years and older and its link with diabetes characteristics [9]. In a previous report, we showed that microvascular complications were common at baseline in elderly diabetic patients and were significantly associated with HbA1c, geriatric disorders and some individual characteristics [10]. More recently, we found that mortality over five years was associated with cardiovascular complications, especially heart failure [11].

The present report addresses the microvascular complications in the 987 patients of the GERODIAB cohort, their progression during the five-year follow-up, and the association of these factors with five-year mortality.

Material and Methods

From June 2009 to July 2010, 987 consecutive ambulatory type 2 diabetic outpatients (52.1% women) aged 70 years and over were included from 56 French diabetic centres. The centres were selected from voluntary French reference diabetic centres after stratification on the French regional areas using a random procedure. Type 2 diabetic patients in France are usually managed by General Practitioners (GPs), and are referred at least once a year to a regional reference centre, mainly for an annual check-up. The centres were chosen so that a total of 1000 patient were included over one year. This number of patients was estimated from previous epidemiologic data in order to achieve 90% power with a significant relative risk of 1.5 in the subgroup with high HbA1c, and to provide a representative sample of at least 0.1% of French type 2 diabetic patients aged ≥70 years. Ambulatory patients referred by their usual practitioners (mainly GPs) for an annual check-up or for specialized advice in ambulatory care were eligible. Included patients were required to be sufficiently autonomous, which was defined as having an Activities of Daily Living (ADL) score≥ 3 [12]. Patients had to give informed consent to participate in the study. All consecutive eligible patients attending the centre over one year were included in the study.

The patients' clinical history of diabetes and associated diseases were recorded at inclusion. Due to the observational nature of the survey, management and follow-up measures were those defined in European and French recommendations [13,14], including recording HbA1c levels at inclusion and then every 3 months. An estimation of the Glomerular Filtration Rate (eGFR) was performed using the MDRD (Modification of Diet in Renal Disease) equation. It was recorded at inclusion and then every 6 months. Urinary albumin excretion was measured every year. Microalbuminuria was defined either as an excretion of >30 mg/day on 24-hour urine collection, or as an excretion of >30 mg/g of creatinine on spot collection. Eye fundus examination was performed at baseline and then every year during follow-up. Peripheral neuropathy was studied at a physical examination performed annually using motor and sensory testing that included assessments of pinprick, vibration and temperature, sensory perception with a 10g monofilament, and ankle reflex testing. Other laboratory parameters and the cardiac (including resting ECG) and geriatric evaluations with specific scales [12] were performed at inclusion and then every 12 months. Complementary explorations could be performed by investigators depending on the patients' needs and according to recommendations [8,13,14]. As the study was non-interventional, the glycaemic control objectives and the treatments used were determined by the investigators according to recommendations [14]. A more detailed description of the methodology has been presented previously [9-12].

Retinopathy was classified into three groups: proliferative, non-proliferative, and no retinopathy. Nephropathy was first classified into 5 groups using the MDRD: <15, [15-30, [30-45, [45-60, and ≥60 mL/min. The last group was separated into two subgroups based on the presence of microalbuminuria: an MDRD ≥60 mL/min with microalbuminuria, and an MDRD ≥60 mL/min without microalbuminuria [15,16]. Because of the small number of patients with an MDRD <15 mL/min (Table 1), they were grouped with patients with MDRD levels in the [15-30 mL/min range. Peripheral neuropathy and macular oedema were classified as "Yes" or "No".

	Population n=987	Lost to Follow-up n=131 (13·3)	Died or Completed n=856 (86·7)	P (Lost vs. Others)	Died n=207 (21·0)	Completed n=649 (65·8)	P (Died vs. Completed)
Retinopathy							
Proliferative	90 (9.1)	9 (6.9)	81 (9.5)		22 (10.6)	59 (9.1)	
Non-Proliferative	156 (15.8)	20 (15.3)	136 (15.9)		30 (14.5)	106 (16.3)	
No	741 (75.1)	102 (77.9)	639 (74.6)	0.6	155 (74.9)	484 (74.6)	0.69
Macular Oedema							
Yes	33 (3.3)	7 (5.3)	26 (3.0)		8 (3.9)	18 (2.8)	
No	954 (96.7)	124 (94.7)	830 (3.0)	0.19	199 (96.1)	631 (97.2)	0.43
Nephropathy: MDRD (mL/min)							

<15	4 (0.4)	0 (0.0)	4 (0.5)		3 (1.4)	1 (0.2)	
[15-30[	22 (2.2)	4 (3.1)	18 (2.1)		8 (3.9)	10 (1.5)	
[30-45[	104 (10.5)	17 (13.0)	87 (10.2)		27 (13)	60 (9.2)	
[45-60[	177 (17.9)	28 (21.4)	149 (17.4)		40 (19.3)	109 (16.8)	
≥60 with Microalbuminuria	190 (19.3)	17 (13.0)	173 (20.2)		40 (19.3)	133 (20.5)	
≥60 without Microalbuminuria	490 (49.6)	65 (49.6)	425 (49.6)	0.28	89 (43.0)	336 (51.8)	0.012
Peripheral Neuropathy							
Yes	278 (28.2)	40 (30.5)	238 (27.8)		79 (38.2)	159 (24.5)	
No	709 (71.8)	91 (69.5)	618 (72.2)	0.52	128 (61.8)	490 (75.5)	0.0001
Values are numbers (%).							

Table 1: Microvascular complications at inclusion during a 5-year follow-up.

For multivariate hazard ratio analyses, simple "Yes/No" grouping variables were defined for retinopathy by combining the proliferative and the non-proliferative subgroups. For nephropathy, the choice of the cut-off point for the combination was based on the results of the survival analysis, in which groups were defined according to the best survival rates. This procedure is described in the results section.

Statistical Analyses

Values were expressed as medians [Interquartile Range (IQR)] or percentages. The cumulative value of a quantitative variable was defined for each patient as the mean value over the five-year follow-up. For qualitative variables, the highest grade of severity observed during follow-up was first obtained for each patient; a "Yes/No" cumulative variable was defined for hazard ratio regressions.

Comparisons between groups were done using the Kruskal-Wallis test and the Chi-squared test (Fisher's exact test for small samples). Survival was studied using the Kaplan-Meier method, and survival curves were compared with the Breslow-Gehans generalised Wilcoxon test. Multivariate analyses were done using Cox proportional hazards regression models with stepwise forward and backward procedures. Cumulative variables, as defined previously, were used in these models. SAS 9·4 software (Cary, NC, USA) was used for computations.

Results

The 987 patients included in the study were 77 [73-80] years old (median [IQR]); 36.7% were between the ages of 75 and 80 years, and 28.5% were 80 years and older. They had had diabetes for 16 [10-25] years. Their BMI was 29 [26-33] kg/m² and their blood pressure (SBP/DBP) was 140 [128-150] /73 [67/80] (90% using cardiovascular drugs). The HbA1c was 56 mmol/mol [50-65] (7.3% [6.7-8.1]), and the LDL cholesterol was 2.33 mmol/L [1.81-3.10] (0.90 g/L [0.70-1.20]) (63% of patients treated with statins). Insulin was used by 58% of patients and oral drugs by 71%, including metformin (49%), sulfonylurea (29%), glinides (15%) and DPP4 inhibitors (10%) (others <10%). A more detailed description of the population at inclusion can be found in Table 2.

	Population n=987	**Lost to Follow-up n=131 (13.3%)**	**Died or Completed n=856 (86.7%)**	**P (Lost vs. Others)**	**Died n=207 (21.0%)**	**Completed n=649 (65.8%)**	**P (Died vs. Completed)**
Age (year)	77 [73–80]	77 [73–81]	77 [73–80]	0.28	79 [75–83]	76 [73–79]	<0.0001
Men/Women	473 (47.9) / 514 (52.1)	49 (37.4) / 82 (62.6)	424 (49.5) / 432 (50.5)	0.01	112 (54.1) / 95 (45.9)	312 (48.1) / 337 (51.9)	0.13
BMI (kg/m²)	29.3 [26.0–32.8]	28.7 [25.7–32.0]	29.4 [26.1–32.9]	0.11	29.4 [25.4–32.9]	29.3 [26.4–32.9]	0.48

Waist-to-Hip Ratio >1 men or >0.8 women	673 (68.2)	98 (74.8)	575 (67.2)	0.08	126 (60.9)	449 (69.2)	0.03
Alcohol consumption	318 (32.2)	39 (29.8)	279 (32.6)	0.52	85 (41.1)	194 (29.9)	0.003
Tobacco consumption	36 (3.6)	4 (3.1)	32 (3.7)	0.99	7 (3.4)	25 (3.9)	0.76
High School	180 (18.2)	22 (16.8)	158 (16.0)	0.6	32 (15.5)	126 (19.4)	0.67
Institutional living	38 (3.9)	3 (2.3)	35 (4.1)	0.32	14 (6.8)	21 (3.2)	0.03
Hypertension	884 (89.6)	117 (89.3)	767 (89.6)	0.92	187 (90.3)	580 (89.4)	0.69
Systolic blood pressure (mmHg)	140 [128-150]	140 [127-151]	140 [128-150]	0.91	140 [130-150]	140 [128-150]	0.83
Diastolicarterial pressure (mmHg)	73 [67-80]	75 [70-80]	73 [67-80]	0.22	71 [65-80]	74 [68-80]	0.14
Orthostatic hypotension	292 (29.6)	38 (29.0)	254 (29.7)	0.88	65 (31.4)	189 (29.1)	0.53
Cholesterol Risk Factor	871 (88.2)	107 (81.7)	764 (89.3)	0.11	182 (87.9)	582 (89.7)	0.48
LDL cholesterol (mmol/L)	2.33 [1.81-3.10]	2.59 [1.94-3.21]	2.38 [1.84-2.95]	0.08	2.43 [1.91-2.97]	2.35 [1.84-2.92]	0.54
Triglycerides (mmol/L)	1.34 [1.01-1.90]	1.41 [0.95-2.03]	1.37 [1.01-1.83]	0.68	1.36 [1.03-1.98]	1.37 [0.99-1.80]	0.49
HbA1c (mmol/mol)	56 [50–65]	56 [50–65]	56 [50–65]	0·86	57 [51–66]	56 [50–65]	0·26
Duration of Diabetes (year)	16 [10–25]	17 [8–24]	16 [10–25]	0.33	15.5 [10–25]	16 [10–25]	0.99
Fasting blood glucose (mmol/L)	7.2 [6.1–9.4]	7.2 [6.1–8.9]	7.2 [6.1–9.4]	0.79	7.2 [6.1–10.0]	7.2 [6.1–9.4]	0.61
Capillary glucose controls/week	14 [5–21]	14 [3–21]	14 [6–21]	0.09	14 [3–21]	14 [7–21]	0.19
Hypoglycaemia last 6 months	333 (33.7)	52 (39.7)	281 (32.8)	0.12	62 (30.0)	219 (33.7)	0.31
Hyperosmolarity	3 (0.3)	1 (0.8)	2 (0.2)	0.35	1 (0.5)	1 (0.2)	0.43
Ketosis	9 (0.9)	1 (0.8)	8 (0.9)	0.99	2 (1.0)	6 (0.9)	0.99
Heart failure	90 (9.1)	10 (7.6)	80 (9.3)	0.53	36 (17.4)	44 (6.8)	<0.0001
Coronary insufficiency	291 (29.5)	31 (23.7)	260 (30.4)	0.12	77 (37.2)	183 (28.2)	0.01
Rhythms dysfunction	67 (6.8)	8 (6.1)	59 (6.9)	0.74	30 (14.5)	29 (4.5)	<0.0001
Conduction abnormality	219 (22.2)	24 (18.3)	195 (22.8)	0.25	59 (28.5)	136 (21.0)	0.02
Repolarisation abnormality	138 (14)	16 (12.2)	122 (14.3)	0.53	33 (15.9)	89 (13.7)	0.42
Cerebrovascular involvement	151 (15.3)	24 (18.3)	127 (14.8)	0.3	43 (20.8)	84 (12.9)	0.006
Peripheral vascular disease of lower limbs	249 (25.2)	28 (21.4)	221 (25.8)	0.28	72 (34.8)	149 (23.0)	0.0007
Foot wound	50 (5.1)	9 (6.9)	41 (4.8)	0.31	22 (10.6)	19 (2.9)	<0.0001
Amputation	20 (2.0)	1 (0.8)	19 (2.2)	0.5	12 (5.8)	7 (1.1)	0.0003

History of Infection	129 (13.1)	18 (13.7)	111 (13.0)	0.81	36 (17.4)	75 (11.6)	0.03
Associated disease	235 (23.8)	30 (22.9)	205 (23.9)	0.79	70 (33.8)	135 (20.8)	0.0001
ADL <6	258 (26.1)	36 (27.5)	222 (25.9)	0.71	91 (44.0)	131 (20.2)	<0.0001
IADL <14	548 (55.5)	66 (50.4)	482 (56.3)	0.2	154 (74.4)	348 (50.5)	<0.0001
Cognitive disorders *	260 (26.3)	38 (29.0)	222 (25.9)	0.46	77 (37.2)	145 (22.3)	<0.0001
Screening MNA<14	503 (51.0)	81 (61.8)	422 (49.3)	0.008	126 (60.9)	296 (45.6)	0.0001
Mini-GDS >0	233 (23.6)	30 (22.9)	203 (23.7)	0.84	56 (27.1)	147 (22.7)	0.19
At least one Oral Antidiabetic Drug	699 (70.8)	92 (70.2)	607 (70.9)	0.87	133 (64.3)	474 (73.0)	0.02
Metformin	483 (48.9)	66 (50.4)	417 (48.7)	0.72	70 (33.8)	347 (53.5)	<0.0001
A-glucosidase inhibitor	49 (5.0)	4 (3.1)	45 (5.3)	0.28	13 (6.3)	32 (4.9)	0.45
DPP IV inhibitor	99 (10.0)	21 (16.0)	78 (9.1)	0.014	12 (5.8)	66 (10.2)	0.057
Glitazones	72 (7.3)	12 (9.2)	60 (7.0)	0.38	11 (5.3)	49 (7.6)	0.27
Glinides	144 (14.6)	14 (10.7)	130 (15.2)	0.17	43 (20.8)	87 (13.4)	0.01
Sulfonyl ureas	282 (28.6)	39 (29.8)	243 (28.4)	0.74	51 (24.6)	192 (29.3)	0.17
GLP1 analogues	47 (4.8)	7 (5.3%)	40 (4.7%)	0.74	12 (5.8%)	28 (4.3%)	0.38
GLP1 analogues or OAD	704 (71.3%)	92 (70.2%)	612 (71.5%)	0.77	136 (65.7%)	476 (73.3%)	0.03
Insulin	568 (57.5%)	72 (55.0%)	496 (57.9%)	0.52	131 (63.3%)	365 (56.2%)	0.07
Statins	622 (63.0)	67 (51.1)	555 (64.8)	0.0025	124 (59.9)	431 (66.4)	0.09
Values are number (%) or median [IQR];*MMSE<25 or dementia							

Table 2: Patients at inclusion according to their follow-up over 5 years.

During the follow-up, 131 (13.3%) patients were lost, including 29 (2.9%) patients who voluntary stopped the study; 649 (65.8%) patients completed the study, and 207 (21.0%) died (Table 1). Patients lost to follow-up did not differ for the most part from the others at baseline; however, many significant differences were found between the patients who died and those who completed the survey (Table 2). Microvascular complications did not differ significantly in the patients lost to follow-up compared to the others (Table 1). They were more frequent among patients who died during the follow-up compared to those who survived, with the exception of eye complications (Table 1).

Evolution of Microvascular Complications

At five years, a mild increase was found in the frequency of retinopathy, from 24.9% to 28.0% (Table 3). The frequency of macular oedema increased from 3.3 to 8.8%. Microalbuminuria increased from 50.4 to 74.7%, mild nephropathy (MDRD <60 mL/min) from 31.1 to 51.6%, and severe nephropathy (MDRD <30 mL/min) from 2.6 to 8.5%. A great increase was also found in the frequency of peripheral neuropathy (28.2 to 48.0%; Table 3).

	Inclusion	1 year	2 years	3 years	4 years	5 years
Retinopathy						
Proliferative	90 (9.1)	106 (10.7)	112 (11.3)	118 (12.0)	123 (12.5)	131 (13.3)
Non-Proliferative	156 (15.8)	186 (18.8)	209 (21.2)	223 (22.6)	235 (23.8)	244 (24.7)
No	741 (75.1)	695 (70.4)	666 (67.5)	646 (65.5)	629 (63.7)	612 (62.0)
Macular Oedema						

Yes	33 (3.3)	44 (4.5)	59 (6.0)	69 (7.0)	78 (7.9)	87 (8.8)
No	954 (96.7)	943 (95.5)	928 (94.0)	918 (93.0)	909 (92.1)	900 (91.2)
Nephropathy: MDRD (mL/min)						
<15	4 (0.4)	6 (0.6)	6 (0.6)	10 (1.0)	11 (1.1)	14 (1.4)
[15-30[	22 (2.2)	35 (3.5)	50 (5.1)	58 (5.9)	66 (6.7)	70 (7.1)
[30-45[	104 (10.4)	132 (13.4)	142 (14.4)	156 (15.8)	166 (16.8)	181 (18.3)
[45-60[	177 (17.9)	220 (22.3)	230 (24.1)	244 (24.7)	248 (25.1)	244 (24.7)
≥60 with Microalbuminuria	190 (19.3)	224 (22.7)	234 (23.7)	226 (22.9)	225 (22.8)	218 (22.1)
≥60 without Microalbuminuria	490 (49.6)	370 (37.5)	317 (32.1)	293 (29.7)	271 (27.5)	260 (26.3)
Peripheral Neuropathy						
Yes	278 (28.2)	355 (36.0)	390 (39.5)	423 (42.9)	450 (45.6)	474 (48.0)
No	709 (71.8)	632 (64.0)	597 (60.5)	564 (57.1)	537 (54.4)	513 (52.0)
Values are numbers (%).						

Table 3: Evolution of cumulative values of microvascular complications in the 987 patients over 5 years.

Associations with Survival

Diabetic retinopathy was slightly but not significantly associated with poor survival (P=0.57; Figure 1). Macular oedema was not significantly associated with survival (P=0.56).

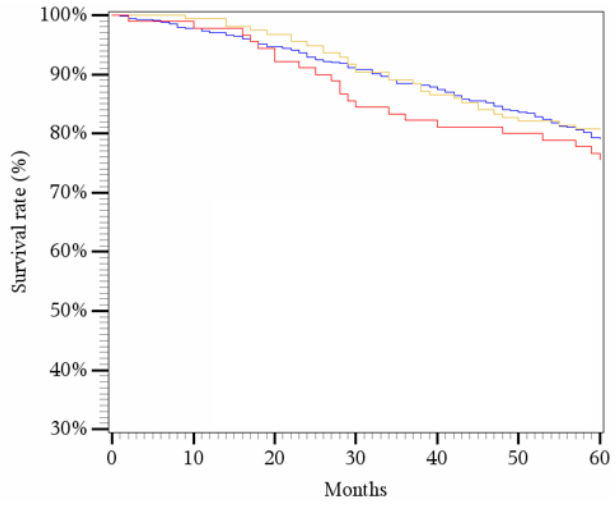

Figure 1: Survival over five years in 987 patients with proliferative retinopathy (red line), with non-proliferative retinopathy (yellow line) or without retinopathy (blue line); (P=0.57)

Conversely, a strong association was found between nephropathy and mortality, with survival rates at five years schematically decreasing when the MDRD decreased (P=0.026, Figure 2). Patients with an MDRD <30 mL/min had a lower survival rate than others; patients with an MDRD≥60 mL/min without microalbuminuria had the best survival. The best association with survival was observed when the population was separated into two groups using a cut-off point of 30 mL/min (P=0.0083).

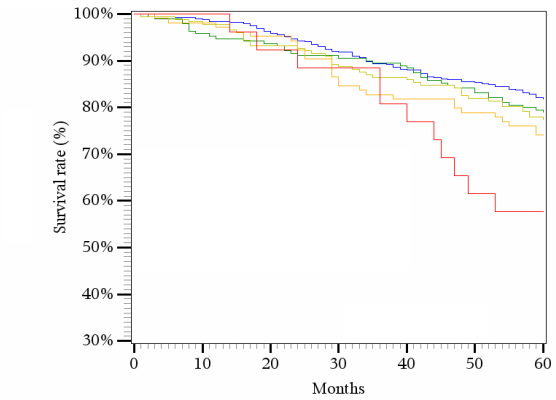

Figure 2: Survival over five years in 987 patients with MDRD <30 mL/min (red line), in the range [30-45[mL/min (orange line), [45-60[mL/min (yellow line), or≥60 mL/min with microalbuminuria (green line) and or≥60 mL/min without microalbuminuria (blue line; P=0.026)

Peripheral neuropathy was also strongly associated with a lower survival rate (P=0.0003, Figure 3).

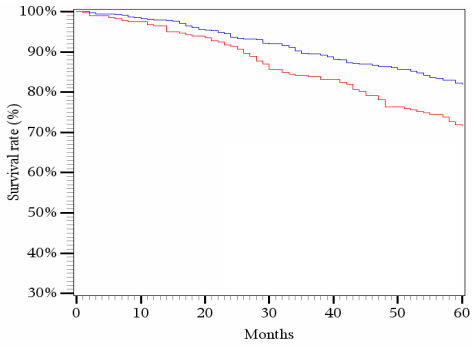

Figure 3: Survival over five years in 987 patients with peripheral neuropathy (red line) or without peripheral neuropathy (blue line); (P<0.0001).

Multivariate Hazards Ratios

Microvascular complications were analysed simultaneously using Cox proportional hazards. In the multivariate model using an MDRD <30mL/min, severe nephropathy was the only significant predictor of death (HR=1.75, CI=1.24-2.03, chi²=8.74, P=0.0029). Microvascular complications were also tested in a model including all significant degenerative complications of diabetes (Table 1). In this model, heart failure was included first (HR=1.96, CI=1.45-2.64, chi²=19.49, P<0.0001), followed by amputation (HR=2.04, CI=1.25-3.35; chi-square=8.08, P=0.0045) [11]. Nephropathy did not remain a significant predictor of the outcome after the inclusion of heart failure.

Discussion

The first aim of our study was to describe the microvascular complications, their progression over five years and their association with survival in elderly type 2 diabetic patients with a median age of 77 years. We found a large increase in the frequency of microvascular complications from inclusion to five years. All complications were involved. Mild nephropathy (MDRD <60 mL/min) increased from 31 to 52%, and severe nephropathy (MDRD <30 mL/min) from less than 3% to more than 8%. Peripheral neuropathy increased from 28 to 48%. Retinopathy increased "only" from 25 to 38%, and macular oedema from 3 to 9%. Although approximately one-quarter of the diabetic patients were aged 75 years or above [1-2], the natural progression of microvascular complications remains uncertain and has been seldom studied in this age range. This is likely related to the recent increase in life expectancy in the general population and the difficulty in managing studies in elderly patients [12,17]. The results provide important information, but should be considered according to the treatments taken by patients, especially antidiabetic, metabolic and cardiovascular drugs (Table 1). The natural progression of the disease itself without the preventive effect of drugs would probably result in more complications. On the other hand, our results reflect real-life progression in patients treated according to the recommendations, and underline the influence of diabetes on microvascular events despite up-to-date preventive treatments, suggesting that the management of diabetes and its complications can still be improved.

All the microvascular complications under study were significantly associated with survival, with the exception of eye complications (retinopathy and macular oedema).Nephropathy and peripheral neuropathy were very strongly associated with mortality. Severe nephropathy associated with an MDRD <30mL/min was strongly associated with poor survival in univariate analysis. But it only concerned a small group of patients. An interesting point is that nephropathy did not remain a significant predictor of death when macrovascular complications, and especially heart failure, were considered simultaneously in the model. This suggests that some information included in nephropathy was also included in heart failure, and supports the strong association reported previously between these diabetic complications [18,19]. Our results supported these strong association at baseline (P<0.0001) [10,11], which remained in term of competitive risk over the follow-up. In addition, the fact that severe nephropathy only concerned a small group of patients could explain that its power to predict mortality was lower than that of heart failure in the multivariate analysis of the population. Therefore, severe nephropathy should be considered in individual prediction of the outcome.

Microalbuminuria should be considered separately. This marker is difficult to manage, and fluctuations are commonly observed in repeated measurements in all diabetic patients [15,16]. In elderly patients, the assay is difficult to perform, and the reliability of the results is not certain, even when spot collections are used, as in our study. Many factors can induce false positive or false negative results, including urine infections, and variations in hydration and urine concentration [15]. Regardless of the assays used to diagnose nephropathy, it is commonly believed that its frequency is underestimated compared with real histological lesions involving the kidney [20]. This can limit its predictive value on mortality, which was not clear in our study. Microalbuminuria, as with nephropathy, has been reported to be associated with hypertension and macrovascular complications, and to be predictive of cardiovascular risk [18,19].

Peripheral neuropathy was also found to be a main predictor of poor survival in our study. It was evaluated at least annually with physical examinations, which were supplemented by electrodiagnostic testing only when the investigator deemed it necessary based on the individual situation. In addition, an entire physical examination can be long and difficult to perform in elderly patients, and therefore the real frequency of peripheral neuropathy may be underestimated in our study [21]. On the other hand, neuropathy can be induced by such other conditions, as alcohol consumption and several associated diseases and/or treatment drugs [22]. The diagnosis of diabetic neuropathy therefore cannot be confirmed in our patients. However, the association with poor survival observed in our study supports the importance of evaluating peripheral neuropathy in elderly diabetic patients. It probably has a major influence on the daily lives of these patients, especially with regard to lifestyle. In our study, autonomic neuropathy was not assessed because of the difficulty in evaluating cardiac, gastrointestinal and genitourinary dysfunctions in elderly patients [23].

Eye complications, including retinopathy and macular oedema, did not appear to be significantly associated with mortality in our study. This has been commonly, although inconstantly, reported [8]. Here too, retinal photography was not performed

systematically and could explain some false negative results. It is of note, however, that most of our patients were treated with antihypertensive drugs and had close to normal blood pressure values (Table 1). This could result in a lower occurrence of eye complications in our population [24]. This could also explain the lower frequency of deaths related to hypertensive complications, and associated with retinopathy. On the other hand, eye complications remain a major cause of impairment of quality of life and autonomy, and their occurrence should be prevented, even if they do not impair survival.

In our study, Cox multivariate proportional hazard models were used to compare the different associations observed between microvascular complications and mortality. Nephropathy was found to be the strongest predictor of mortality. Obvious conclusions should however be considered with caution, because many treatments and interventions could improve the evolution of the other complications under study. These treatments were likely to have been used in our patients, as 90% of them were treated with cardiovascular drugs at inclusion, 63% with statins and 7% with fibrates; 12% received anticoagulants, and 56% platelet aggregation inhibitors. These drugs could have prevented the occurrence of some complications, including retinopathy and macrovascular complications, and therefore could have interfered with our results [24,25]. Classical risk factors such as hypertension and hypercholesterolemia were thus managed in our patients (Table 1). In addition, these risk factors were strongly associated with cardiovascular complications and nephropathy at inclusion [10,11]. These are probably the reasons that they were not shown to be factors significantly associated with death in our survey. Risk factors adjustments were not performed in our study, since numerous factors would have to be considered; the stepwise multivariate Cox method was preferred, including all factors significantly associatedwith death (Table 1).

Our study is observational and its results should be considered with caution. Consecutive outpatients were recruited, with the only specific exclusion criterion being a very low level of autonomy. Many French centres included patients, but these centres are specialized and not at the primary level involving GPs. As a result, some patients may have been overlooked during the recruitment process. However, most diabetic patients are referred at least once a year to specialized centres by GPs for an annual check-up, and recruitment bias is not likely to have concerned many patients. Some patients, including those with less severe forms of diabetes, could be managed only by GPs. These patients do not necessarily follow the French recommendations and could have been overlooked in our study. On the other hand, GPs also refer patients with acute conditions for standard hospitalizations, and these patients should not have been included in our study. Therefore, the population under study may be considered a relatively representative sample of elderly autonomous French type 2 ambulatory diabetic patients without acute complications and who are managed according to recommendations, accounting for about 0.1% of the French diabetic patients in this age range [26].

Another limitation of our study is the percentage of patients (13.3%) lost to follow-up. This is not an excessive number compared to previous studies involving younger patients, considering that outpatient follow-up may be difficult in elderly patients owing to their decreased autonomy or cognitive alterations, or when living far from diabetes centres [5,6,8]. However, the patients lost to follow-up did not differ significantly from the other patients except for gender and a mildly impaired nutritional status, which were not significantly associated with survival (On-line Supplementary Table S 1).

In summary, a strong association was found in our study between poor survival in elderly type 2 diabetic patients and both nephropathy and peripheral neuropathy, nephropathy being the strongest predictor of adverse outcome. In our population, nephropathy was strongly associated with heart failure, which had the highest predictive value for mortality. Interventional studies designed to improve kidney and nerve dysfunctions should be performed in elderly diabetic patients.

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- **In-Text Appendix 1: Study Investigators**

H. Affres, M. Alix, F. Archambeaud, Z. Barrou, B. Bauduceau, P. Beau, S. Beltran, C. Benoit, J.-P. Beressi, F. Bernachon, C. Berne, G. Blaimont, J.-F. Blickle, M. Boda-Buccino,J. Bohatier, P. Böhme, L. Bordier, K. Bouchou, B. Bouillet, F. Bouilloud, R. Bouix,E. Boulanger, I. Bourdel-Marchasson, C. Bourgon, E. Bourrinet, P. Brocker, I. Bruckert, C. Capet, C. Carette, B. Cariou, A. Carreau, C. ChaillouVaurie, S. Chamouni, C. Ciangura, C. Collet-Gaudillat, M.-E. Combes-Moukhovsky, T.Constans, M. Cordonnier, A. Cuperlier, D. Dambre, J. D'Avigneau, P. De Botton, V. Degros, F. Delamarre-Damier, S. Denat, F. Desbiez,B. Deumier,F. Dorey,J. Doucet, E. Dresco, A. Drutel, E. Du Rosel De Saint Germain, D. Dubois-Laforgue, B. Duly-Bouhanick, O. Dupuy, L. Dusselier, S. Faucher-Kareche, S. Fendri, P. Fontaine, S. Galinat, H. Gin, F. Glaise, T. Godeau, B. Gonzalez, I. Got, B. Guerci, P.-J. Guillausseau, S. Hadjadj, Y. Hadjali, M. Halbron,S. Halimi,C. Halter,H. Hanaire, V. Hardy,A. Hartemann-Heurtier, J.-P. Haulot, F. Hequet, M. Issa-Sayegh, P. Jan, N. Jeandidier,H. Joseph-Henri, I. Julier,V. Kerlan, T. Kharitonnoff, M. Ladsous, L.

Lahaxe, M.-P. Lamaraud, E. Lassenne, J.-M. Lecerf, P. Lecomte,I. Leroux,S. Lesven, M. Levy, S. Lopez ,F. Makiza, P. Manckoundia, C. Marquis Pomeau, H. Mayaudon, S. Micheli, R. Mira, F. Monnier, H. Mosnier-Pudar, N. Neri, I. Normand, M. Paccalin, C. Pagu,D. Paris,A. Penfornis, J.-L. Perie,J.-M. Petit,G. Petit Aubert, B. Pichot-Duclos, L. Pivois, M. Popelier, G. Poulingue, M. Priner, Dr V. Quipourt, M. Rasamisoa, J.-L. Richard, V. Rigalleau, N. Roudat, C. Sanz,J.-M. Serot, D. Sifi,S. Sirvain, A. Slimani, E. Sonnet, C. Sosset, A. Soualah, A. Stroea, I. Tauveron, J. Timsit, M.Tschudnowsky, A.Vambergue, O.Verier-Mine, C. Verny, M. Virally†.

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