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Brief Communication

Does albuminuria predict renal risk and/or cardiovascular risk in obese type 2 diabetic patients?

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Abstract: Increased urinary albumin excretion (UAE) is a marker of renal and cardiovascular risk in patients with type 2 diabetes (DT2). What about the obese patient with DT2? Does albuminuria predict the progression of renal disease and/or cardiovascular disease? The objective of this study is to determine the link between albuminuria, renal risk and cardiovascular risk in a cohort of obese DT2 patients. This is a prospective study begun in September 2006. It included DT2 patients presenting obesity defined by a body mass index (BMI)>30 Kg/m^2. Three groups of patients were defined: normo-albuminuria (Urinary Albumin Excretion UAE<30 mg/day or Albumin Creatinine Ratio ACR<30 mg/g), micro-albuminuria (UAE=30-300 mg/day or ACR=30-300 mg/g) and macro-albuminuria (UAE>300 mg/day or ACR>300 mg/g). Data on 144 obese DT2 patients were compiled: The mean age of our patients was 59 ± 9 years and the sex ratio 0.26. The incidence of ESRD was higher in the macro-albuminuria group than in the two other groups (26.5% vs. 1.2%, p<0.001). The incidence of cardiovascular events was 15.4%, 14.3% and 23.5% in the normo, micro and macro-albuminuria groups (p=0.48). A history of cardiovascular comorbidities was the main cardiovascular risk in multivariate analysis (0R=15.07; 95% CI=5.30-42.82; p<0.001) and the low admission GFR (0R=5.67; 95% CI=1.23-9.77; p=0.008) was the main factor for progression of kidney disease in multivariate analysis. Albuminuria may be a better marker of kidney disease progression than of cardiovascular risk in the obese DT2 patient, according to our results. However, to accurately demonstrate the link albuminuria - renal risk and albuminuria - cardiovascular risk in the obese DT2 patient, additional studies using very strict criteria of selection and judgment are needed.

Keywords: Diabete type 2, obesity, albuminuria, renal risk, cardiovascular risk

Introduction

Patients with type 2 diabetes mellitus (DT2) and micro- or macro-albuminuria incur a risk for cardiovascular death that is 2-12 times that observed in patients with less albuminuria [1, 2]. Increasing values of urinary albumin excretion are also a major risk factor for progression of kidney diseases in DT2 [3].

What about the obese patient with DT2? Does albuminuria predict the progression of renal disease and/or cardiovascular disease? The objective of this study is to determine the link between albuminuria and renal risk on the one hand, and cardiovascular risk on the other hand in a cohort of obese DT2 patients.

Materials and methods

This is a prospective study begun in September 2006, conducted at the Reference Center of Chronic Diseases of Oujda, Morocco (Eastern Morocco, North Africa). The study included DT2 patients presenting obesity defined by a body mass index (BMI)>30 Kg/m^2. It excluded DT2 patients presenting end stage renal disease (ESRD) on admission and/or another renal pathology, other than diabetes, that could explain the renal impairment, and type 1 diabetic patients. Patients were followed for a minimum of 36 months and a maximum of 60 months. Various data including sociodemographic (age, gender), clinical (blood pressure, duration of diabtes, medications use Vascular

Table 1. Comparison of clinical and biological parameters at the time of enrollment and renal and cardiovascular complications occurred during follow-up in obese type 2 diabetic patients (n=144)

Variable	Normo-albuminuria N=26	Micro-albuminuria N=84	Macro-albuminuria N=34	P
At admission:				
Follow-up, months*	50 ± 8	50 ± 10	43 ± 14	0.007
Female, n (%)	18 (62.2)	64 (76.2)	24 (70.6)	0.65
Body mass index, Kg/m^{2}*	33.8 ± 3.3	33.4 ± 3.1	34.1 ± 3.5	0.55
Morbid obesity, n (%)	7 (26.9)	18 (21.4)	9 (26.5)	0.76
Age, years*	61 ± 11	57 ± 9	62 ± 9	0.008
Duration of diabetes, years#	4 (2, 10)	7 (3, 11)	10 (4, 18.5)	0.02
Family history of diabetes, n (%)	16 (61.5)	59 (70.2)	22 (64.7)	0.66
History of vascular co-morbidities, n (%)	4 (15.4)	12 (14.3)	8 (23.5)	0.46
Arterial hypertension n (%)	14 (53.8)	47 (56)	26 (76.5%)	0.08
Diabetic retinopathy, n (%)	6 (23.1)	37 (44)	18 (52.9%)	0.03
Diabetes treatment				
Insulin, n (%)	9 (34.6%)	55 (65.5)	30 (88.2)	<0.001
Diabetes pills, n (%)	22 (84.6%)	70 (83.3)	16 (47.1)	<0.001
Use of statin, n (%)	12 (46.2)	37 (44)	18 (52.9)	0.68
Use of ACE inhibitors and/or ARBs, n (%)	23 (88.5)	79 (94)	32 (94.1)	0.53
Systoliv blood pressure (SBP), mmHg*	146 ± 19	141 ± 19	148 ± 20	0.17
Diastolic blood pressure (DBP), mmHg*	82 ± 13	77 ± 11	79 ± 12	0.14
Use > 2 antihypertensive drugs, n (%)	13 (50)	50 (59.5)	26 (76.5)	0.09
GFR estimated by MDRD, ml/min/1.73m^{2}#	89 ± 19	91 ± 26	61 ± 34	<0.001
GFR by MDRD (<60 ml/min/1.73m^{2}), n (%)	2 (7.7)	11 (13.1)	20 (58.8)	<0.001
UAE (urinary albumin excretion), mg/day#	16 (10, 23)	78 (62, 134)	675 (370, 1307)	<0.001
Total cholesterol, g/L*	2.03 ± 0.33	2.02 ± 0.45	2.13 ± 0.59	0.47
HDL-C, g/L*	0.45 ± 0.08	0.44 ± 0.07	0.41 ± 0.07	0.16
LDL-C g/L*	1.16 ± 0.24	1.12 ± 0.36	1.26 ± 0.38	0.27
Triglycerides, g/L*	1.41 ± 0.61	1.47 ± 0.76	1.50 ± 0.87	0.89
Hb_{A1C}, %*	7.9 ± 1.3	8.6 ± 1.8	8.1 ± 1.7	0.15
Hemoglobin, g/dl*	13.4 ± 1.7	13.1 ± 1.3	12.0 ± 1.6	0.002
A the end of the follow-up:				
GFR by MDRD (<60 ml/min/1.73m^{2}), n (%)	2 (7.7)	19 (22.6)	20 (58.8)	<0.001
End stage renal disease, n (%)	0 (0)	1 (1.2)	9 (26.5)	<0.001
Vascular co-morbidity events, n (%)	4 (15.4%)	12 (14.3)	8 (23.5)	0.48

*Variables expressed as mean ± SD (standard deviation), #variables expressed as median IQR (interquartile range).

comorbidity) and biochemical parameters (serum creatinine, Hb A1c, hemoglobin, cholesterol, triglycerides and urinary albumin excretion (UAE) or Albumin creatinine ratio (ACR) were collected at admission and were performed for each patient every year [4]. The UAE or ACR parameters were considered positive based on at least 2 to 3 urine samples and independent of any urinary infection.

Patients were considered for the presence or absence of vascular co-morbidities such as ischemic heart disease (history of angina or myocardial infarction or cardiac revascularization or cardiomyopathy) and/or peripheral vascular disease (amputation and/or gangrene of the lower limbs). Glomerular filtration rate (GFR) was estimated using the abbreviated Modification of Diet in Renal Disease (MDRD) formula.

Three groups of patients were identified: Group 1 (normo-albuminuria), Group 2 (micro-albuminuria) and Group 3 (macro-albuminuria). Microalbuminuria was defined as UAE=30-300 mg/day or ACR=30-300 mg/g and macro albuminuria by UAE>300 mg/day or ACR>300 mg/g.

Statistical analysis

All Statistical calculations were done by computer using SPSS software (statistical package for the Social Sciences, version 13.0). Quantitative variables were expressed as means ± SD or as medians and interquartile range, depending on their distribution. The comparison of quantitative variables between 3 groups was performed by ANOVA test if the quantitative variable showed symmetrical distribution or by the Kruskal Wallis test if the quantitative variable showed asymmetrical distribution. Comparison of qualitative variables between 3 groups was done using the chisquare test. Tests were 2-tailed, with significance set at a *p* value of less than 0.05. Results were reported with odds ratio (OR) and 95% confidence interval (CI). Binary logistic regression was used to identify risk factors in univariate and multivariate analysis.

Results

Data on 144 obese DT2 patients were studied. The mean age of our patients was 59 ± 9 years and the sex ratio 0.26. Morbid obesity was found in 23.6% of cases. Arterial hypertension was observed in 60.4% of cases, diabetic retinopathy in 42.4% of cases, active tobacco use in 6.2% of cases, and only 11.8% had health insurance.

On admission, 18.1% (26 cases), 58.3% (84 cases) and 23.6% (34 cases) of patients had normo- micro- and macro-albuminuria respectively. Clinical and biological data at admission for the first nephrology consultation are reported in **Table 1** according to the stage of albuminuria. Patients with macro-albuminuria were older, had a longer duration of diabetes, a higher frequency of diabetic retinopathy, greater use of insulin, and a lower admission eGFR compared to the two groups of normo-and micro-albuminuria.

In contrast, there was no statistically significant difference between the three groups of patients on admission concerning the frequency of arterial hypertension, history of cardiovascular comorbidities and lipid parameters.

Renal and cardiovascular complications occurring during follow-up are also reported in **Table 1**. The incidence of ESRD was higher in the macro-albuminuria group than in the normoand micro-albuminuria groups. Moreover, there was no statistically significant difference between the three groups with regard to the occurrence of cardiovascular events.

At the end of follow-up, albuminuria was negative in 26.4% (38 cases), at the stage of micro-albuminuria in 60.4% (87 cases) and at the stage of macro-albuminuria in 13.2% (19 cases). There was progression from the normo stage to the micro-albuminuria stage in 53.8% of cases and a regression from the macro stage to the micro-albuminuria stage in 52.9% of cases.

Concerning the risk factors for occurrence of cardiovascular events among obese DT2 patients, the following were not identified as cardiovascular risk factors by univariate analysis: age (OR=1.01; 95% CI=0.96-1.06; p=0.66), duration of diabetes (OR=1.02; 95% CI=0.96-1.09; p=0.38), arterial hypertension (OR=2.53; 95% CI=0.95-6.77; p=0.06), diabetic retinopathy (OR=0.99; 95% CI=0.42-2.35; p=0.99), UAE (OR=1.00; 95% CI=0.99-1.00; p=0.60) and GFR on admission (OR=0.99; 95% CI=0.98-1.01; p=0.84). However, the following were identified as cardiovascular risk factors by univariate analysis: History of cardiovascular comorbidities (OR=16.51; 95% CI=15.87-46.40; p<0.001) and statin use (OR=3.95; 95% CI=1.54-10.14; p=0.004).

Only a history of cardiovascular comorbidities was identified as the principal factor for occurrence of cardiovascular events in multivariate analysis (OR=13.88; 95% CI=4.82-39.97; p<0.001).

Concerning the factors of progression for chronic kidney disease (eGFR<60 ml/min/1.73 m^2) in obese DT2 patients, age (OR=1.08; 95% CI=1.04-1.12; p<0.001), duration of diabetes (OR=1.12; 95% CI=1.05-1.19; p<0.001), UAE (OR=1.00; 95% CI=1.00-1.00; p<0.001) and admission eGFR (OR=1.00; 95% CI=1.00-1.00; p<0.001) were identified in univariate analysis as risk factors for progression of kidney disease. Arterial hypertension (OR=6.46; 95% CI=0.79-52.46; p=0.08) and glycolated hemoglobin (OR=1.03; 95% CI=0.84-1.27; p=0.73) were not identified as risk factors in univariate analysis.

In multivariate analysis, we identified only admission eGFR (OR=5.67; 95% CI=1.23-9.77;

p=0.008) as the main factor for progression of kidney disease in our cohort.

Discussion

Diabetic nephropathy is a leading cause of ESRD worldwide and about one-third of patients with DT2 has micro- or macro-albuminuria [4]. Furthermore, micro- and macro-albuminuria were associated with increased renal and cardio vascular risk [5]. What about obese DT2 patients? Very few studies have been published on this subject. However, the incidence of micro- or macro albuminuria in obese DT2 patients reported by some studies was between 35 and 45% [6, 7]. The incidence in our study was 81.9%. That is a high value, which may be explained in part by the selection criteria, involving patients sent to nephrology consultation who are not only at high risk of renal impairment, but who are also seen at a late stage because of the absence of early detection of kidney disease in this population. Wentworth et al observed that obesity was significantly associated with the prevalence of albuminuria in both men and women with DT2, but without specifying the stage of UAE [8].

Furthermore, albuminuria remains a modifiable factor on which one can act. Lowering of the UAE rate can be achieved with treatment and this allows reduction of the risk of kidney disease progression. In our study, the rate of negativation was 22.8%, the regression rate 52.9% and the progression rate 11.7%. While the regression of micro-albuminuria is classic in DT2, regression of macro-albuminuria to microor normo-albuminuria is rarer. In our study, that regression occurred in 52.9% and 14.7% of cases respectively and in 60% in an Australian series of obese DT2 patients after laparoscopic adjustable gastric banding [6].

What about renal risk in the obese DT2 patient? It has previously been shown that there is a significant relationship between degree of proteinuria and risk for progression to ESRD [9]. This relationship has not been a particular focus of study among obese DT2 patients, and by extrapolation of data, one might suppose that albuminuria is correlated with the progression of diabetic nephropathy (DN) among obese patients as well. Most studies have analyzed the progression of DN through comparison of the obese vs. the non-obese. Thus, renal risk has not been evaluated using only a cohort of obese DT2 patients, and in relation to the stage of albuminuria. The literature tells us that BMI is not correlated with the progression of DN and that renal risk remains similar, whether the DT2 patients are obese or non-obese [10, 11]. However, is albuminuria itself a factor of prediction and of independent DN progression in obese patients? In our study, progression to chronic renal failure (eGFR<60 ml/min/1.73 m^2) to the terminal stage was greater in the macro-albuminuria group than in the normo- and micro-albuminuria groups.

What about cardiovascular risk? In our study, we did not find a statistically significant difference between the three groups of patients with regard to cardiovascular events occurring during follow-up, even if the percentages appear higher in the group of obese patients with macro-albuminuria. Ruggenenti et al. observed through the BENEDICT study that a history of comorbidities and the UAE were cardiovascular risk factors in multivariate analysis of a cohort of DT2 patients with normo-albuminuria, whereas the BMI was not identified as a risk factor in univariate or multivariate analysis [12].

Conclusion

The obese DT2 patient is at high risk for both renal and cardiovascular disease. According to our results, albuminuria may be a better marker of kidney disease progression than of cardiovascular risk in the obese DT2 patient. However, to accurately demonstrate the link albuminuria - renal risk and albuminuria - cardiovascular risk in the obese DT2 patient, additional studies using very strict criteria of selection and judgment are needed.

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Disclosure of conflict of interest

The authors report no conflicts of interest.

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