original article

Prevalence and determinants of albuminuria in a cohort of diabetic patients in Lebanon

Nadine Taleb,[a] Haytham Salti,[b] Mona Al-Mokaddam,[a] Marie Merheb,[a] Ibrahim Salti,[a] Mona Nasrallah[a]

From the [a]Department of Internal Medicine, Endocrinology and the [b]Department of Ophthalmology, American University of Beirut, Beirut, Lebanon

Correspondence and reprints: Mona Nasrallah, MD · Department of Internal Medicine, Endocrinology · American University of Beirut · PO Box 11-0236/D23, Beirut, Lebanon · T: +961-135-0000 ext. 5322 · mn36@aub.edu.lb · Accepted for publication September 2008

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BACKGROUND AND OBJECTIVES: Few data are available on the extent of albuminuria in diabetic populations in the Middle East generally and in Lebanon specifically. We conducted this study to determine the prevalence of albuminuria and its major risk factors in a cohort of diabetic patients in Lebanon.

PATIENTS AND METHODS: Diabetic patients followed in the outpatient department at the American University of Beirut Medical Center (AUBMC) were included in a prospective observational study. AUBMC is a tertiary referral center and the outpatient department typically handles patients of low socioeconomic status with advanced disease. Patients were classified according to their urinary albumin-to-creatinine ratio (ACR) as having normoalbuminuria (ACR<30 mg/g creatinine), microalbuminuria (ACR=30 to <300 mg/g creatinine), or macroalbuminuria (ACR ≥300 mg/g creatinine). The three groups were compared to analyze the association between albuminuria and its risk factors. In addition, independent predictors of albuminuria were determined using multivariate logistic regression and presented as an odds ratio.

RESULTS: Microalbuminuria and macroalbuminuria were present in 33.3% and 12.7% of 222 patients (mean age 56.4 years, mean deviation of diabetes 8.6 years, 58.7% women, 43.8% obese), respectively. Factors significantly associated with microalbuminuria included glycemic control, insulin use, and total and LDL cholesterol. Those associated with macroalbuminuria included in addition to glycemic control and insulin use, duration of diabetes, hypertension, elevated mean arterial pressure (MAP), and presence of neuropathy, retinopathy and peripheral vascular disease by bivariate analysis. Only glycemic control was an independent risk factor for both in addition to MAP and retinopathy for macroalbuminuria by multivariate analysis.

CONCLUSION: Albuminuria is highly prevalent among this cohort of diabetic patients in Lebanon. Both glycemic control and blood pressure need to be better targeted in its management.

Diabetic nephropathy (DN) is a grave complication of both types of diabetes. In most parts of the world DN has become the most common cause of end-stage renal disease.[1,2] The prevalence of DN and its complications is expected to rise as the incidence of diabetes increases worldwide, especially in developing countries.[3] The earliest clinical sign of DN is an increase in urinary albumin excretion that progresses to overt proteinuria and then to renal failure at a rate of 2% to 3% per year.[4] The mortality rate increases significantly as the stage of albuminuria worsens.[5] Multiple risk factors interact in the development and progression of albuminuria including hypertension, glycemic control, diabetes duration, dietary protein overload and genetic predisposition.[6,7] Other less consistent factors like smoking, hypercholesterolemia, obesity and anemia have also been associated with a higher risk of albuminuria.[8]

There is some variability in the prevalence of albuminuria and the degree of contribution of each of its risk factors among different diabetic populations. Few data are available about the extent of this major health problem in the Middle East generally and in Lebanon specifically. Such information is needed because screening for DN and its risk factors allows for the introduction of early interventions to slow or reverse its progression and decrease the rate of its complications.[6,9,10] The aim of the present study was to determine the prevalence of albuminuria and its major risk factors in a cohort of Lebanese diabetic patients. The study was conducted at the American University of Beirut Medical Center

(AUBMC), a major referral center for patients from different parts of Lebanon.

PATIENTS AND METHODS

This report is an analysis of cross-sectional data taken at recruitment for a prospective, observational study involving patients who come regularly to the diabetes clinic in the outpatient department (OPD) of AUBMC. The OPD is a low-budget clinic and as such, the patient population is of a low socioeconomic status with a usually poor educational level. The methods have been described in detail elsewhere along with the epidemiology of this cohort.[11] In this clinic, patients are assessed by the clinical fellows in the division of endocrinology and metabolism under the supervision of an endocrinologist. Patients were eligible if they could be followed for three consecutive years. Exclusion criteria included gestational diabetes mellitus, age <18 years and inability to complete the laboratory data, retinal exam and follow-up visits needed. Patients were recruited consecutively until the target number was reached.

A complete history was taken including known duration of disease, smoking status, and medications used, in addition to a complete physical examination with measurements of height, weight, and blood pressure. Microvascular complications were assessed and defined in the following manner: albuminuria was assessed by collecting a morning urine sample to calculate the albumin-to-creatinine ratio (ACR). Patients were classified according to ACR as having microalbuminuria (ACR=30 to <300 mg/g creatinine) and macroalbuminuria (ACR ≥300 mg/g creatinine). Patients with normoalbuminuria were compared to those with micro- and macroalbuminuria. Retinopathy was assessed by an ophthalmologist who performed a dilated slit lamp fundus exam. Neuropathy was assessed by symptom history and/or the finding of decreased pressure sensation by the monofilament test. Macrovascular complications were considered present or absent according to the history provided by the patient and a review of the medical chart. A subject was considered to have coronary artery disease (CAD) if there was a history of a previous coronary event, including angina or myocardial infarction or a coronary artery intervention (angioplasty or coronary by-pass surgery). Peripheral vascular disease (PVD) included any typical history of lower extremity claudication, the finding of decreased arterial pulses by physical exam, revascularization procedure or radiological evidence of peripheral arterial disease. Cerebrovascular disease included a history of transient ischemic attack or stroke diagnosed by a physician regardless of absence of residual neurological deficit on physical exam. Patients were considered hypertensive if they were already receiving antihypertensive medications or if they were found in the clinic to have elevated blood pressure (SBP >130 mm Hg, DBP >80 mm Hg) and mean arterial pressure was calculated for each patient. The use of angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB) was also assessed in the patients according to hypertension and albuminuria status. An electrocardiogram was obtained on all patients. Fasting venous blood was sampled in all patients from the antecubital vein for the measurement of glycated hemoglobin (HbA_{1c}), serum glucose, creatinine, total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides. Based on the American Diabetes Association 2007 recommendations, subjects were considered to have good control of their glucose levels if their HbA_{1c} was ≤7%. Serum creatinine was considered to be normal if it were ≤1.4 mg/dL in females and ≤1.5 mg/dL in males. All venous blood and urinary tests were collected and performed at the central laboratory of AUBMC using standardized automated techniques. All laboratory testing was done at AUBMC under similar conditions with the following methodology: HbA_{1c} by HPLC (Bio-Rad); urine ACR by the Tina-quant albumin test and immunoturbidimetric assay (Hitachi 912 analyzer, Roche Diagnostics); serum creatinine by the Jaffe method using the kinetic, rate-blanked and compensated assay (Hitachi 912 analyzer, Roche Diagnostics); total cholesterol, HDL-cholesterol and triglyceride by Hitachi 912 analyzer (Roche Diagnostics). The study was approved by the Institutional Review Board of AUBMC in accordance with the Helsinki Declaration and all patients included in this study signed a written informed consent.

Data are reported as mean±standard deviation, or as absolute numbers and percentages. Based on their ACR ratio, subjects were divided into 3 categories: normoalbuminuria, microalbuminuria and macroalbuminuria with cut-offs as described above and comparisons were made against the normoalbuminuria group. The associations between albuminuria and the different characteristics of the study population were performed as bivariate analyses using the chi-square test for categorical variables or t-test for metric variables and one-way ANOVA for variables with multiple levels. Factors that showed a significant association with either microalbuminuria and macroalbuminuria in a bivariate analysis were entered into a logistic regression to identify the independent risk factors for the development of either microalbuminuria or macroalbuminuria. However, MAP was used instead

Table 1. Bivariate analysis of patients (n=222) according to albuminuria status.

	Normoaibuminuria (n=120)	Microalbuminuria (n=74)	*P*	Macroalbuminuria (n=28)	*P´*
Age (years)	56.7±11.5	56.3±12.7	.83	56.1±11.5	.81
Gender (female)	78 (65.0%)	39 (52.7%)	.09	15 (53.6%)	.26
BMI (kg/m^2)	30.2±5.7	29.6±5.6	.53	30.8±5.3	.62
Duration of disease (years)	7.6±6.5	9.2±7.6	.12	11.0±6.6	.014
Insulin use	24 (20.2%)	25 (33.8%)	.035	12 (42.9%)	.012
Ever smoker	39 (32.8%)	37 (50.7%)	.71	16 (57.1%)	.40
HBA_{1c} (%)	7.9±2.0	9.2±2.5	< .001	9.2±2.9	.03
Neuropathy	39 (32.8%)	34 (46.6%)	.056	16 (57.1%)	.02
Retinopathy	30 (25.9%)	26 (38.2%)	.08	17 (60.7%)	<.001
Coronary artery disease	17 (14.3%)	17 (23.3%)	.11	6 (21.4%)	.35
Cardiovascular disease	5 (4.2%)	3 (4.1%)	1.00	2 (7.1%)	.51
Peripheral vascular disease	14 (11.8%)	16 (21.9%)	.06	12 (42.9%)	<.001
Total cholesterol (mmol/L)	4.7±1.1	5.3±1.3	.004	4.9±1.1	.19
LDL cholesterol (mmol/L)	2.8±0.9	3.3±1.2	.005	3.0±0.8	.42
HDL cholesterol (mmol/L)	1.3±0.4	1.2±0.3	.38	1.1±0.4	.15
Triglyceride (mmol/L)	1.9±1.4	1.9±1.0	.83	3.1±3.5	.09
Hypertension	56 (46.7%)	39 (52.7%)	.41	23 (82.1%)	.001
SBP (mm Hg)	127.7±18.7	130.7±17.8	.32	147.75±21.4	<.001
DBP (mm Hg)	77.2±11.4	79.0±10.0	.28	87.7±10.7	<.001

Data are mean±SD or numbers and percentages; *P* value compares microalbuminuria with normoalbuminuria; *P´* value compares macroalbuminuria with normoalbuminuria

of SBP and DBP because the linearity between these two variables removes their potential effect. The results are presented as odds ratios with 95% confidence intervals. A *P* value <.05 was considered to be significant. Statistical Software Package SPSS (version 15.0) was used.

RESULTS

Of 313 patients originally recruited between August 2005 and April 2007, 222 (71%) completed all the requirements of the study including the lab tests, medical interview, physical and comprehensive ophthalmologic exam and electrocardiogram. The mean age of subjects was 56.4±11.7 years. One hundred thirty-two (59.4%) were female and 208 (93.6%) had type 2 diabetes. The mean duration of disease at the time of recruitment was 8.6±6.9 years. Ninety-seven (43.8%) patients were obese (BMI ≥30) and 78 (35%) were current smokers. At the time of recruitment, two-thirds of subjects had an uncontrolled HbA_{1c} of >7%. Hypertension was present in 118 (53.2%) of patients, of whom 83% were receiving either an ACEI or an ARB. Normal ACR was present in 54.0% of patients. Renal function was assessed by serum creatinine levels and was normal in the normoalbuminuria group. Elevated serum creatinine levels were found in 2.5% and 1.5% of the microalbuminuria and macroalbuminuria groups, respectively (data not shown).

The rate of microalbuminuria was 33%. In the bivariate analysis, total and LDL cholesterol (but not HDL cholesterol or tryglycercides), and insulin use and poor glycemic control (elevated HbA_{1c}) were associated with microalbuminurea (Table 1). In the multivariate analysis, only HbA_{1c} was found to be an independent risk factor for microalbuminuria (Table 2). For each 22% higher risk for each 1% increase in HbA_{1c}. An ACEI or ARB was used in 43.8% of patients with microalbuminuria. The rate of macroalbuminuria was 12.7% (Table 1). In the bivariate analysis, duration of disease, insulin use, HbA_{1c}, neuropathy, retinopathy, perpheral vascular disease, and hypertension were significantly associated with macroalbuminuria. An ACEI or ARB was used in 71.4% of patients with acroalbuminuria. In the multivariate analysis, only HbA_{1c} as an independent risk factor for microalbuminuria (Table 2).

For every 1% increase in HbA_{1c}, there was a 22% higher risk of microalbuminuria (odds ratio 1.22, 95% confidence interval 1.1- 1.4, *P*=.007). When restricting the analysis to patients with macroalbuminuria, HbA_{1c}, MAP and retinopathy were identified as independent risk factors. For every 1% increase in HbA_{1c}, there was a 1.5 times higher risk of macroalbuminuria (odds ratio 1.54, 95% confidence interval 1.07-1.46, *P*=.003). The odds of macroalbuminuria among patients with retinopathy and PVD were 5.72 and 4.89 times, respectively. The odds of macroalbuminuria among patients free of these two complications (OR 6.3, 95% CI 1.3-30.8, *P*=.022 and OR 5.72, CI 1.16-28.11, *P*=.032 respectively). However, it should be noted that despite the high odds ratio for PVD the result cannot be interpreted as significant because the confidence interval reaches 1.00. For every 10 mm Hg rise in MAP, there is 2.43 times higher risk of macroalbuminuria (odds ratio 2.43, 95% CI 1.36-4.37, *P*=.003).

Table 2. Independent factors associated with diabetic nephropathy.

	Variables	Odds ratio	95% confidence interval	*P* value
Microalbuminuria	HbA_{1c} (per 1% increase)	1.22	1.1-1.4	.007
Macroalbuminuria	MAP (per 10 mm Hg increase)	2.43	1.36-4.37	.003
	HbA_{1c} (per 1% increase)	1.54	1.16-2.05	.003
	Retinopathy	5.72	1.16-28.11	.032
	Peripheral vascular disease	4.89	1.00-24.13	.050

Other factors included in the regression model but not included in table are: insulin use, TC and LDL for microalbuminuria, hypertension, neuropathy, duration of diabetes and insulin use for macroalbuminuria.
*CI for PVD reached 1.00 and therefore should be interpreted as of borderline significance despite the *P* value.

DISCUSSION

This study found a high rate of albuminuria in this cohort of diabetic patients at a tertiary medical center in Lebanon. The prevalence of 33.2% and 12.7% for micro- and macroalbuminuria, respectively, is higher than that reported for the UKPDS (United Kingdom Prospective Diabetes Study) population, where the prevalence was 25% and 5% for micro and macroalbuminuria, respectively.[5] Of note is that a higher ACR range (50-299 mg/gram creatinine) for defining microalbuminuria and a slightly higher mean duration of disease were reported in the UKPDS group than in our patients. It may be argued that the prevalence of albuminuria may be overestimated in our subjects because it was based on a single sample of urinary ACR. However, our rates were also higher than a diabetic population from Chennai, India where, as in our study, the diagnosis of albuminuria was based on a single ACR of greater than 30 mg/g creatinine.[12] One explanation for the higher rate may be that acute hyperglycemia increased the rate of microalbuminuria, especially since two-thirds of our patients had poor glycemic control, as defined by HbA_{1c}. Nevertheless, none of these arguments accounts for the higher prevalence of macroalbuminuria. A likely explanation may be the long duration of the disease and the poorer state of control among this cohort with low socioeconomic status. Genetic predisposition may also play a role.

The risk factors for diabetic kidney disease in this study were in accordance with the known traditional risk factors, especially for macroalbuminuria. Thus, glycemia, BP control, the presence of other microvascular disease, and duration of disease were significant risk factors for macroalbuminuria in our subjects.[8] Of these factors, only glycemic control, as assessed by HbA_{1c}, reached statistical significance when restricting analysis to patients with microalbuminuria. The association between microalbuminuria and glycemia was very strong (*P*<.001) as compared to that with macroalbuminuria (*P*=.03), again emphasizing the more direct relationship between poor glycemic control and microalbuminuria. Acute hyperglycemia will increase glomerular filtration rate and intraglomerular pressure, causing an increased leakage of microalbumin.

Surprisingly, there was no association between microalbuminuria and blood pressure control. One pos-

sible explanation is poor glycemic control (rather than blood pressure) being the main driving factor of microalbuminuria for this group. Another explanation is that 83% of subjects with hypertension were taking ACEIs or ARBs, possibly normalizing albumin excretion. Other risk factors associated with microalbuminuria were total serum cholesterol and LDL-C. One postulated mechanism for the link between hyperlipidemia and nephropathy is low-grade inflammation.[13] This effect was not seen among the macroalbuminuria group, possibly because of the small sample size, with only 28 patients in this study having macroalbuminuria.

The presence of a microvascular complication puts the subject at high risk of having other diabetic complications.[8] Retinopathy is a well-established risk factor in type 1 diabetes, and remains a strong predictor of nephropathy in type 2 diabetes, although other factors such as genetics and hypertension may attenuate this relationship.[14] There was a trend for an association with retinopathy in the microalbuminuria group, without reaching significance again possibly because of the acute hyperglycemia being the main determinant in this group. Macrovascular disease is also associated with albuminuria, but less so than microvascular complications and in this study only PVD was associated with macroalbuminuria. One explanation is the lower rate of macrovascular complications in general, and thus, numbers did not reach statistical significance. Furthermore, the diagnosis of CAD was based on known disease by history or ECG findings and may have been underestimated.

Less well-established risk factors that were not significant in this study include age, smoking and obesity. A higher BMI was associated with a higher risk of chronic kidney disease in some studies, unlike in ours. This might be due to poor glycemic control favoring weight loss in our patients.[15] A recent study found the association to be significant, specifically with waist circumference in diabetic patients, a variable not assessed in our cohort.[16] Smoking is a risk factor for the development and progression of albuminuria.[17,18] Among our patients with micro- or macroalbuminuria, higher percentages were either current or ex-smokers without reaching statistical significance. Insulin use was also associated with albuminuria (both micro and macro). However, this relationship disappears in the logistic regression. Therefore, insulin use was probably a confounding marker of very poor glycemic control and duration of disease. Only 20% of patients were taking insulin, whereas 68% had HbA_{1c} above target.

In the logistic regression analysis, the variable that remained an independent predictor of both groups was HbA_{1c}, which is in accordance with other studies.[12] Thus, glycemic control is a crucial target in preventing diabetic kidney disease. In addition, blood pressure control (as represented by MAP) and retinopathy remained independently associated with macroalbuminuria. Blood pressure control, a well-known risk factor, remains a strong predictor, because the use of ACEIs or ARBs for the hypertensive group is unlikely to have totally reversed the macroalbuminuria, if already existing. As a more advanced stage of diabetic nephropathy, macroalbuminuria is also expected to be associated with advanced complications of DM such as retinopathy.

To our knowledge, there are no published estimates on the prevalence of DN or its predictors among diabetic subjects in Lebanon. The high prevalence found may be an overestimation of the true prevalence, as mentioned, first because microalbuminuria was based on a single ACR determination. Second, AUBMC is a tertiary care center with a patient population that has a high level of morbidity. Third, the OPD, serves patients from a low socioeconomic background who present late into their disease and are undertreated. Even though this study does not estimate the community prevalence of albuminuria, the high levels found in our patient population call for urgent action because of the known risk to progression into renal failure and development of CAD.[19] This study may have overestimated the extent of microalbuminuria and thus the results are not generalizable to the overall community. The small sample size may have missed certain associations, especially with macroalbuminuria. Finally certain predictors were not assessed in this study like genetic predisposition to DN and dietary protein intake. However, risk factors found were in accordance with previous reports. Furthermore, protein intake is more important in the progression than actual development of albuminuria and is not expected to be an important risk factor in our population. The diet in Lebanon among middle-aged subjects tends to remain 'Mediterranean', which is not very high in protein, especially animal protein.

This study is the first to measure albuminuria rates in a tertiary medical center in Lebanon and to correlate it with diabetic risk factors. The very high rates found necessitate further investigation into potential causes. The 3-year follow-up data, once available, will provide a better evaluation of this health problem. Nevertheless, the main predictors found so far, HbA_{1c} and BP levels, need to be tightly controlled to minimize diabetic albuminuria with its known complications.

Disclosure

The epidemiology of type 2 diabetes in our cohort has been

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