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Original Article

Does smoking increase the risk of progression of nephropathy and/or cardiovascular disease in type 2 diabetic patients with albuminuria and those without albuminuria?

Yassamine Bentata[1], Ilham Karimi[1], Nawal Benabdellah[1], Fatiha El Alaoui[1], Intissar Haddiya[1], Redouane Abouqal[2,3]

[1]Department of Nephrology, Medical School of Oujda, University Mohammed The First, Oujda, Morocco; [2]Department of Medical Emergency, Ibn Sina University Hospital, 10000, Rabat, Morocco; [3]Laboratory of Biostatistics, Clinical and Epidemiological Research, Medical School University Mohamed V, Rabat, Morocco

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Abstract: Diabetic nephropathy is the primary cause of chronic kidney disease and is associated with increased cardiovascular mortality. Cigarette smoking is probably the most complex and the least understood among the risk factors for chronic kidney disease and cardiovascular disease in diabetic patients. The aim of this study was to determine the impact of smoking on progression of nephropathy and cardiovascular disease in type 2 diabetic patients with albuminuria and those without albuminuria. Methods: This is a prospective study. The Ethics Committee of Morocco's Mohammed V University in Rabat approved the study protocol. Inclusion criteria targeted patients who were type 2 diabetics and who had nephrology follow up for at least 36 months. Results: A total of 671 cases of T2D were included. Mean age of all patients was 65 ± 11 years and 12.1% were smokers. There was no statistically significant difference between T2D patients with albuminuria according to absence of presence of smoking at the time of enrollment, at 1 year and 3 years of follow-up, concerning the median albumin excretion rate (mg/day): 98 [56-281] vs. 124 [56-323] (p=0.59); 98 [56-281] vs. 124 [56-323] (p=0.15) and 98 [56-281] vs. 124 [56-323] (p=0.52) respectively. There was a statistically significant difference between T2D patients with albuminuria according to absence or presence of smoking at the time of enrollment and the end of follow-up, concerning cardiovascular events: 56 (12.3%) vs. 19 (28.4%) (p<0.001) and 66 (14.5%) vs. 19 (28.4%) (p=0.004) respectively. Conclusion: Smoking remains one of the most important modifiable risk factors for progression of renal and cardiovascular disease in diabetic patients, thus adding to the burden of morbimortality.

Keywords: Smoking, type 2 diabetes, renal progression, cardiovascular disease

Introduction

Cigarette smoking is now recognized as an important independent risk factor in the progression of chronic kidney disease (CKD) including diabetic nephropathy and of cardiovascular diseases (CVD). It contributes by increasing the rate of transition from microalbuminuria to persistent proteinuria and promoting the progression to End Stage Renal disease [1-3]. Cigarette smoking is probably the most complex and the least understood among the risk factors for CKD and CVD because cigarette smoke contains thousands of different chemical components. Nicotine, the main component of cigarettes, has a variety of biological effects that may play an important role in the pathogenesis of vascular and renal disease by promoting atherosclerosis and angiogenesis [4].

The aim of this study was to determine the impact of smoking on progression of nephropathy and cardiovascular disease in type 2 diabetic patients with albuminuria and those without albuminuria.

Methods

This is a prospective study started in January 2009 and conducted at the Reference Center for Chronic Diseases in Oujda, Morocco (Eastern Morocco). The Ethics Committee of Morocco's Mohammed V University in Rabat approved the

Table 1. Comparison of clinical and biological parameters between four groups of patients with T2D according to the presence or not of smoking and albuminuria at the time of enrollment and at the end of the study

Parameters (n=671)	Group 1 Smoking - Albuminuria - (n=137)	Group 2 Smoking + Albuminuria + (n=67)	Group 3 Smoking - Albuminuria + (n=453)	Group 4 Smoking + Albuminuria - (n=14)	*P*-Value
At the time of enrollement					
Age at diabetes diagnosis, years*	64 ± 11	64 ± 10	66 ± 12	66 ± 12	0.43
Duration of diabetes, years#	8 [10, 15]	10 [13, 18]	9 [14, 19]	7 [9, 13.5]	<0.001
Body mass index, kg/m^2*	28.18 ± 4.72	26.28 ± 3.51	28.67 ± 4.68	27.68 ± 4.05	0.001
History of cardiovascular disease, n (%)	8 (5.8)	19 (28.4)	56 (12.4)	1 (7.1)	<0.001
History of hypertension, n (%)	48 (35)	31 (46.3)	260 (57.4)	2 (14.3)	<0.001
Hypertension, n (%)	39 (28.5)	26 (38.8)	181 (40)	4 (28.6)	0.09
Diabetic retinopathy, n (%)	24 (17.5)	34 (50.7)	181 (40)	1 (7.1)	0.001
Diabetic neuropathy, n (%)	30 (21.9)	29 (43.3)	193 (42.6)	4 (28.6)	<0.001
Albuminuria, ma/day	17 [12, 23]	124 [56, 323]	99 [57, 284]	13 [9, 22]	<0.001
Estimated GFR by MDRD, ml/min/1.73 m^2*	93 ± 21	83 ± 30	85 ± 32	101 ± 23	<0.001
Hemoglobin$_{A1C}$, %*	8.1 ± 1.6	8.7 ± 1.5	8.4 ± 1.9	7.9 ± 1.8	0.002
Triglycerides, g/L*	1.30 ± 0.51	1.47 ± 0.60	1.42 ± 0.64	1.42 ± 0.51	0.16
At the end of the follow-up (36 months)					
Insulin use, n (%)	52 (38)	48 (71.6)	268 (59.2)	5 (36.7)	<0.001
Hypertension, n (%)	27 (19.7)	26 (38.8)	164 (36.2)	2 (14.3)	0.001
Use >2 antihypertensive drugs, n (%)	28 (20.4)	14 (20.9)	170 (37.5)	2 (14.3)	<0.001
Ischemic heart events occurred, n (%)	7 (5.1)	19 (28.4)	66 (14.6)	2 (14.3)	<0.001
Albuminuria, mg/day	16 [11, 23]	76 [54, 230]	83 [43, 219]	13 [8, 20]	<0.001
GFRe par MDRD, ml/min/ 1.73 m^2*	91 ± 22	79 ± 29	81 ± 31	101 ± 20	<0.001
Rapid renal progression, n (%)	10 (7.3)	19 (28.4)	132 (29.2)	0 (0)	<0.001
Hemoglobin$_{A1C}$, %*	7.9 ± 1.6	8.4 ± 1.6	8.1 ± 1.5	7.8 ± 1.1	0.001
Triglycerides, g/L*	1.21 ± 0.41	1.46 ± 0.62	1.34 ± 0.63	1.53 ± 0.71	0.002
Normo-albuminuria (<30 mg/day), n (%)	117 (85.4)	6 (9)	71 (15.7)	12 (85.7)	<0.001

*Variables expressed as mean ± SD (standard deviation), #variables expressed as median IQR (interquartile range). Hypertension was defined par systolic blood pressure >140 mmHg and/or Diastolic blood pressure >90 mmHg. GFRe, glomerular filtration rate estimated by MDRD; MDRD, Modification Diet in Renal Disease.

study protocol (University Mohamed V Souissi, Rabat). Verbal informed consent was required from all participants. Inclusion criteria targeted patients who had confirmed T2D and had been regularly followed in nephrology consultation for at least 36 months. Excluded from the study were those T2D patients who were pregnant, who had a single kidney, a pathology other than diabetes capable of altering renal function (renal lithiases, Polycystic Kidney Disease, prior long-standing arterial hypertension, a neoplasm, long-term use of nephrotoxic medications), End Stage Renal Disease on admission and/or follow-up of less than 24 months. Patients with type 1 diabetes were excluded from this study.

We defined smoker patients as current smokers and ex-smokers who had stopped smoking during the last three years, whatever the duration and dose of smoking.

Cardiovascular events were defined as ischemic heart disease (history of angina, myocardial infarction, heart failure and/or coronary revascularization) and/or peripheral vascular disease (amputation and/or gangrene of the lower limbs) and/or cerebrovascular disease (history of stroke). T2D was diagnosed according to the criteria of the World Health Organization [5]. Albuminuria was measured from at least two 24-hr urine samples and determined as the mean of 24-hr urine collections to minimize variability.

We calculated eGFR with the abbreviated Modification of Diet in Renal Disease (MDRD) Study equation. Rapid progression was defined

as sustained decline in eGFR of more than 5 ml/min/1.73 m^2/year. The rate of eGFR decline (mL/min/1.73 m^2/year) for each patient was determined by: (Last eGFR - Baseline eGFR)/ follow-up period in years.

Data were analyzed using the Statistical Package for Social Sciences version 13.0 (SPSS, Inc., Chicago, IL). Comparison of quantitative variables between four groups was performed using analysis of variance (ANOVA) if the variable was symmetrically distributed or the Kruskal-Wallis test if the variable was asymmetrically distributed. Comparison of qualitative variables between four groups was performed using the chi-square test. All *p* values were two-sided and $p < 0.05$ was considered statistically significant.

Results

A total of 671 cases of T2D were included. The mean age of all patients was 65 ± 11 years. 12.1% of all patients were smokers and 33.3% were obese.

There was no statistically significant difference between T2D patients with albuminuria according to absence or presence of smoking at the time of enrollment, at 1 year and 3 years of follow-up, concerning the median albumin excretion rate (mg/day): 98 [56-281] vs. 124 [56-323] (p=0.59); 98 [56-281] vs. 124 [56-323] (p=0.15) and 98 [56-281] vs 124 [56-323] (p=0.52) respectively.

There was a statistically significant difference between T2D patients with albuminuria according to absence or presence of smoking at the time of enrollment and the end of follow-up, concerning cardiovascular events: 56 (12.3%) vs. 19 (28.4%) (p <0.001) and 66 (14.5%) vs. 19 (28.4%) (p=0.004) respectively.

Table 1 shows the comparison of clinical and biological parameters between four groups of patients with T2D according to the presence or not of smoking and albuminuria at the time of enrollment and at the end of the study.

Discussion

The prevalence of smoking in our study was 12.1% among T2D patients. This prevalence is low in comparison with rates reported by other studies that vary between 12% and 27.4% [6, 7].

In our study, we observed that the prevalence of rapid renal progression was the same in the group of smoker patients with albuminuria and in the group of non-smokers with albuminuria. both prevalences were higher than observed in the group of non-smokers without albuminuria. This confirms the major role of albuminuria in the progression of DN. Feodoroff et al. showed that in T1 diabetes, current smoking was a risk factor for the progression of diabetic nephropathy and the risk increased with the increasing dose of smoking. The authors of this study also demonstrated that ex-smokers seem to carry a similar risk of progression of diabetic nephropathy to that of nonsmokers [3]. Aggarwad et al. showed in their study that increased levels of microalbuminuria have a direct correlation with HbA1c and smoking in T1D patients and T2D patients [8]. Vulgari et al. confirmed in their study that smoking cessation affected microalbuminuria independently from the effect of antihypertensive, hypolipidemic, and diabetic treatment in T2D patients [9].

It is important to note that passive smokers are also at risk of progression of kidney disease similarly to active smokers The National Health and Nutrition Examination Survey (NHANES) also demonstrated a strong association between exposure to secondhand smoke and proteinuria in both diabetics and non-diabetics, suggesting that passive smokers are also at increased risk of chronic kidney disease [10].

However, in our study the prevalence of cardiovascular events occurring during follow-up was higher in the group of smokers with albuminuria than in the other three groups. Thus, cardiovascular risk is higher than renal risk for smokers with T2D than for non-smokers with T2D.

Conclusion

Smoking is one of the most important modifiable risk factors for progression of renal and cardiovascular disease in diabetic patients, thus adding to the burden of morbimortality. While albuminuria has a major role in renal disease progression, smoking seems to play a capital role in cardiovascular disease.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Yassamine Bentata, Department of Nephrology, Medical School of

Oujda, University Mohammed The First, Avenue Hassan II, Rue Kadissia, Numéro 12, Oujda, Morocco Tel: 00212661289940; Fax: 00212536531919; E-mail: bentatayassamine@yahoo.fr

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