Microvascular Research 92 (2014) 79–84

Contents lists available at ScienceDirect

Microvascular Research

journal homepage: www.elsevier.com/locate/ymvre

# Higher risk of microvascular complications in smokers with type 1 diabetes despite intensive insulin therapy

A. Uruska [a,*], A. Araszkiewicz [a], P. Uruski [b], D. Zozulinska-Ziolkiewicz [a]

[a] Department of Internal Medicine and Diabetology, Poznan University of Medical Sciences, Raszeja Hospital, Mickiewicza 2, 60-834 Poznan, Poland
[b] Department of Hypertensiology, Angiology and Internal Medicine, Poznan University of Medical Sciences, Dluga 1/2, 61-848 Poznan, Poland

ARTICLE INFO

*Article history:*
Accepted 3 January 2014
Available online 12 January 2014

ABSTRACT

*Aim:* The aim of the study was to evaluate the relationship between smoking status and the incidence of microvascular complications in patients with type 1 diabetes (DM1), treated with intensive functional insulin therapy (IFIT) from the onset of the disease.
*Methods:* 81 participants (51 men, 30 women) of Poznan Prospective Study (PoProStu) with mean age of 34.0 ± 6.4 years were included in this analysis. Patients were observed for 10.0 ± 1.5 years. Evaluation of microvascular complications of diabetes, such as retinopathy, diabetic kidney disease and neuropathy was performed. Patients were divided into two groups depending on the smoking status: smokers and non-smokers.
*Results:* In the group of smokers (n = 36) in comparison with patients who had never smoked (n = 45) any microangiopathy (58.3% vs 33.3%, p = 0.02), retinopathy (44.4% vs 20%, p = 0.02), diabetic kidney disease (47.2% vs 24.4%, p = 0.03) and neuropathy (25% vs 4.4%, p = 0.02) were found more often. A significant relationship, adjusted for age, sex, duration of diabetes, presence of hypertension and HbA1c between smoking and neuropathy and retinopathy was revealed [OR 10.16 (95%CI 1.59–64.95); p = 0.01 and OR 3.50 (95%CI 1.01–12.12); p = 0.04, respectively].
*Conclusion:* The results show that in patients with DM1, there is a strong relationship between smoking and the diabetic microvascular complications, especially with neuropathy, despite treatment from the initial diagnosis with intensive insulin therapy.



## Introduction

Despite a great progress in the management of the diabetes, it's chronic complications still remain the principal cause of morbidity and mortality. After a 20 year duration of diabetes mellitus type 1 (DM1) almost all patients have different stages of retinopathy (Klein et al., 1984; Krolewski et al., 1986; Lovestam-Adrian et al., 2001), which is responsible for the most cases of blindness (Roy et al., 2004). Moreover, patients with diabetes have a nearly twenty-fold higher risk of kidney injury than patients without diabetes. Diabetic kidney disease is the main cause of kidney failure and need for dialysis (Perneger et al., 1994). Among patients with type 1 diabetes, a cumulative risk of albuminuria after 20 years of diabetes is 20–30% (Krolewski et al., 1985). The presence of albuminuria 8-fold increases the risk of coronary heart disease (Fagerudd et al., 2004; Jensen et al., 1987). Finally, neuropathy significantly decreases the quality of life and is the main cause of non-traumatic lower limb amputations (Vinik et al., 2000).

Nowadays a lot of clinical studies focus on new non-traditional predictors for late diabetic complications. However, we should not forget about traditional risk factors, which seem to be well known. The Diabetes Control and Complications Trial (DCCT) has clearly shown that hyperglycemia plays a crucial role in the development and progression of late diabetic complications (1993). Other parameters that are considered as risk factors for diabetic angiopathy are hypertension, smoking and dyslipidemia (Koivisto et al., 1996; Tseng et al., 2012). All of the above-mentioned factors are potentially modifiable. However, smoking cessation is still a significant clinical problem, difficult to achieve for our patients (Muhlhauser, 1994; Scemama et al., 2006). Moreover it seems that despite the best method of insulin therapy which is intensive insulin therapy, the risk of microvascular complications of type 1 diabetes is highly increased if you smoke cigarettes.

Unfortunately smoking is still a vogue among young people, including type 1 diabetics. Frequency of smoking in this group of patients is comparable with the general population (Sinha et al., 1997). Thus smoking is an important problem in management of type 1 diabetes. It increases the risk of cardiovascular disease among type 1 diabetic patients around 5 times and is connected with higher morbidity (Bishop et al., 2009; Moy et al., 1990; Muhlhauser, 1994; Naskret et al., 2010). In Epidemiology of Diabetes Interventions and Complications (EDIC) trial, a long-term follow-up of the Diabetes Control and Complications

* Corresponding author at: Department of Internal Medicine and Diabetology, Poznan University of Medical Sciences, Raszeja Hospital, Mickiewicza 2, 60-834 Poznan, Poland. Fax: +48 61 8474579.
*E-mail address:* aleksandrauruska@gmail.com (A. Uruska).

0026-2862/$ – see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.mvr.2014.01.002

Trial (DCCT), smoking was one of significant predictors of IMT (intima-media thickness) progression (Polak et al., 2011). A relationship between smoking and microvascular complications is also observed. However, mainly more advanced stages of retinopathy and chronic kidney disease were considered (Chaturvedi et al., 1995; Sawicki et al., 1994; Sinha et al., 1997). In fact data regarding retinopathy and albuminuria are inconsistent. In the German registry of patients with type 1 diabetes, smoking is identified as a risk factor for any retinopathy (OR 1.295), but not for advanced stages of retinopathy (Hammes et al., 2011). Even the protective action of smoking on the retina changes was described (1999; Esteves et al., 2009; Stratton et al., 2001). In the European Diabetes Prospective Complications Study ever smoking was found to be one of the most important predictors of microalbuminuria (Vergouwe et al., 2010). Finally, in the previous studies patients had different disease durations at baseline and were treated with various models of insulin therapy. Our population is under prospective observation and is treated with intensive insulin therapy from the beginning of the disease. Knowledge about the association between smoking and diabetic microangiopathy, especially retinopathy, is still limited and uncertain.

The aim of this study was to assess the relationship between ever smoking status and microvascular complications of diabetes such as: retinopathy, diabetic kidney disease and neuropathy in patients with DM1 treated from the initial diagnosis with intensive insulin therapy.

## Patients and methods

### *Setting and sample*

The study was performed on 81 Caucasian patients (51 men, 30 women), with type 1 diabetes, recruited into the Poznan Prospective Study (PoProStu) in 1994–1999, with a mean age of 34.0 ± 6.4 years, and treated with intensive insulin therapy from the onset of the disease. The group has been assessed once a year in the Department of Internal Medicine and Diabetes, Poznan University of Medical Sciences (Araszkiewicz et al., 2004, 2008; Wegner et al., 2012). The duration of diabetes at follow-up was 10.0 ± 1.5 years.

All subjects were informed about the aim of the study and gave their written consent. The study was approved by the local Ethics Committee (no. 125/08) and is registered on www.ClinicalTrials.gov under no. NCT01411033.

### *Five-day teaching program in intensive insulin therapy*

During the first hospitalization at the diagnosis of diabetes all the patients attended a five-day structured training program in order to acquire the skills for multiple daily insulin injections including adapting short-acting insulin doses before their main meals in accordance with the Diabetes Treatment and Teaching Program (DTTP) (Muller et al., 1999). The course covered the following topics: the nature of diabetes, self-monitoring (which is an integral part of intensive insulin therapy), types of insulin and their action, diet, carbohydrate counting, hypoglycemia and hyperglycemia, sports and exercise, late diabetic complications and self-adjustment of the insulin dose. The training course was conducted by a specially trained nurse educator, a diabetologist, and a dietician. Instruction was delivered in a group setting with a maximum of 10 patients. Additionally, individual support was given in all cases. The objectives were to enable participants to improve their glycemic control, reduce the risk of hypoglycemia, enable dietary and lifestyle freedom, as well as reduce and delay the risk of late diabetic complications.

### *Data collection procedures at the yearly visit*

All the participants completed a standardized questionnaire including details of medical history, duration of diabetes, treatment, smoking status and blood glucose self-control.

All the patients underwent a complete physical examination with anthropometric and blood pressure measurements. Blood pressure was measured twice using the Korotkoff method in a sitting position, after a 10 min rest, using a mercury manometer. We diagnosed arterial hypertension if the mean blood pressure was more than 140/90 mm Hg, or the patient had arterial hypertension diagnosed previously and had received appropriate treatment.

Blood samples were collected, in a fasting state after a period of rest, with minimal occlusion of the vein using the S-Monovette blood collection system. Plasma glucose, serum total cholesterol (TCH), high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, and triglyceride (TG) concentrations were measured using standard methods. HbA1c (glycated hemoglobin) was measured using high-performance liquid chromatography (HPLC) with the Variant Hemoglobin A1c Program (Bio-Rad Laboratories, Hercules, CA, USA). We also assessed mean fasting, and mean 2-hour postprandial glycemia as the mean value of the three following measurements of fasting glycemia and measurements of glycemia 2 h after breakfast, lunch and dinner in the self-assessment profile. The serum C-reactive protein (CRP) concentration was assessed by a highly sensitive microparticle enzyme immunoassay. The test sensitivity was 0.03 mg/l. Serum concentrations of metalloproteinase-9 (MMP-9), myeloperoxidase (MPO), vascular endothelial growth factor (VEGF) and adiponectin were measured with ELISA tests (R&D Systems or Oxis).

### *Smoking status*

Smoking status was self-reported in a questionnaire as current smoker, past-smoker or non-smoker. We determined data about cigarette smoking status for the whole study group. Patients were classified as smokers if they smoked one or more cigarettes daily at the time of follow-up and continue to smoke, and as past-smokers if they had smoked in the past. Patients were also asked at what age they had started and, if they were past-smokers, stopped smoking. Because the group of past-smokers was very small (9 patients), and the mean time without smoking was shorter than 10 years we decided to divide patients into two groups of non-smokers and smokers (current smokers and past-smokers). Lifetime consumption of cigarettes was estimated in pack-years. The clinical characteristics of the two study groups are shown in Table 1.

### *Anthropometric data*

We assessed the body mass index (BMI), waist circumference and waist-to-hip ratio (WHR). The measurement of height and weight was performed using the same medical scales for all the patients. Weight was measured to an accuracy of 100 g and height to 0.5 cm. The waist and hip circumferences were assessed using a non-elastic tape to an accuracy of 1 mm. BMI was calculated using the following equation: BMI = weight (kg) / squared height ($m^2$) and WHR = waist circumference (cm) / hip circumference (cm).

### *Microvascular complications of diabetes outcomes at follow-up*

Screening for diabetic retinopathy was performed by two experienced ophthalmologists using direct ophthalmoscopy through dilated pupils followed, if necessary, by fluorescent angiography. Retinal photographs were taken of each eye using a Fundus Camera VISUSCAM (Zeiss, Germany). After mydriasis of each eye with 1% Tropicamide, stereoscopic 30° color photographs were taken of seven standard fields following the Early Treatment Diabetic Retinopathy Study (ETDRS) criteria (1991). Retinopathy was classified according to the American Academy of Ophthalmology scale as: mild non-proliferative (microaneurysms and hemorrhages only), moderate non-proliferative (extensive microaneurysms, interretinal hemorrhages and hard exudates), severe non-proliferative (venous abnormalities, large blot