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Smokers with type 1 diabetes are more insulin-resistant. Results from Poznan Prospective Study (PoProStu)

ABSTRACT

Aim. The aim of the study was to evaluate the relationship between smoking and insulin resistance in patients with type 1 diabetes (DM1).

Material and methods. The study group consisted of 81 patients with DM1 (51 men, 30 women) from the Poznan Prospective Study (PoProStu), aged 34 ± 6 years, and with diabetes duration 10 ± 1.5 years. Patients were divided into two groups depending on the smoking status: smokers and non-smokers. Insulin resistance was assessed on the basis of indirect parameters such as: estimated glucose disposal rate (eGDR), anthropometric data and liver function.

Results. Smokers (n = 36) in comparison with non-smokers (n = 45) had: higher weight (80.4 ± 14.4 *vs.* 72.9 ± 15 kg, p = 0.02), larger waist circumference (89.6 ± 10.5 *vs.* 83.1 ± 10.9 cm, p = 0.003), higher waist-to-hip ratio (0.9 ± 0.08 *vs.* 0.86 ± 0.09, p = 0.006), higher level of gamma-glutamyl transferase [23 (15–36) *vs.* 15 (11–21) U/l, p = 0.003] and lower eGDR (7.11 ± 2.47 *vs.* 8.82 ± 1.79 mg/kg/min, p = 0.001). A significant relationship, adjusted for age, duration of diabetes, triglycerids (TG) and high density lipoproteins (HDL) cholesterol level between smoking and eGDR < 7.5 mg/kg/min was revealed [odds ratio OR 4.39 (95% confidence interval CI 1.52–12.66); p = 0.005].

Conclusions. The results of this study confirm the healthy dimension of not smoking among people with type 1 diabetes. Smoking in patients with type 1 diabetes, treated from the initial diagnosis with intensive insulin therapy, is associated with insulin resistance. (Clin Diabetol 2018; 7, 2: 122–127)

Key words: diabetes mellitus type 1, glucose disposal rate, insulin resistance, smoking

Introduction

Insulin resistance (IR), characteristic for obesity and type 2 diabetes, is observed more frequently also in patients with autoimmunological background of the disease [1, 2]. Decreased sensitivity to insulin action in patients with diabetes mellitus type 1 (DM 1) is an important clinical problem because IR increases the risk of developing chronic complications of diabetes [1]. Furthermore, IR is a cause of premature death in this group of patients [3].

Insulin resistance is conditioned by both genetic and environmental factors. The most important factor which generates increased resistance to insulin is style of life. Lack of physical activity with overeating are the main causes of abdominal obesity [4]. Visceral adipose tissue is a source of many active substances such as i.e.: free fatty acids, tumor necrosis factor-α, and interleukins, which can impair insulin action [5, 6]. In patients with DM1 experimental studies revealed reduced number of the insulin receptors in adipose tissue and impaired function of glucose transporters

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(GLUT-4) especially in the muscles [7]. Moreover, accumulation of fat in the liver and in the muscles was proved to generate insulin resistance in patients with DM1 [8]. This condition seems to be accelerated by smoking cigarettes [9].

Smoking is an important clinical problem in the population of patients with type 1 diabetes. It's prevalence in young patients is almost the same as in general population. Smoking is generally assumed as risk factor of cardiovascular disease (CVD). A diabetic patient who smokes cigarettes has around 5 fold increased risk of developing cardiovascular disease in comparison with a non-smoker, non-diabetic person [10]. Moreover, CVD is the main cause of death in patients with DM1 [11]. The relationship between smoking and diabetic microangiopathic complications was also described [11, 12]. Finally, smoking influences insulin resistance in patients with type 2 diabetes and in healthy people [13, 14]. The knowledge concerning the influence of smoking on insulin resistance in patients with type 1 DM is still limited. Furthermore, smoking is one of the most difficult risk factors to be modified [10].

The aim of this study was to assess the relationship between smoking status and insulin resistance in patients with DM1 treated with intensive insulin therapy from the onset of the disease.

Material and methods

Setting and sample

The study was performed among 81 Caucasian patients (51 men, 30 women), with type 1 diabetes, recruited into the Poznan Prospective Study (PoProStu; ClinicalTrials.gov Identifier: NCT01411033), in a mean age of 34 ± 6 years, treated with intensive insulin therapy from the onset of the disease. The group has been assessed once a year since 1999 (follow-up period 10 ± 1.5 years). All the subjects were informed about the aim of the study and gave their written consent. The study was approved by the local Ethic Committee. All patients during their first hospitalization at diagnosis of diabetes 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).

Data collection procedures

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

All the patients underwent a complete physical examination with anthropometric measurements and blood pressure check. Blood pressure was measured twice by the Korotkoff method in the sitting position, after 10 minutes 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 had arterial hypertension diagnosed previously and had received appropriate treatment.

Blood samples were collected, in a fasting state using the S-Monovette blood collection system. Plasma glucose, serum total cholesterol (TCH), high density lipoproteins (HDL) cholesterol, low density lipoproteins (LDL) cholesterol, triglycerids (TG) levels and liver function parameters [aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGTP) levels] were measured using standard methods. HbA_{1c} (glycated hemoglobin) was measured using high-performance liquid chromatography with the Variant Hemoglobin A_{1c} Program (Bio-Rad Laboratories, Hercules, CA, USA). Patients had their HbA_{1c} assessed twice a year. The mean value of HbA_{1c} was calculated as the mean value from the results in the years 1999–2007. We also assessed mean fasting (FPG), and mean 2-hour postprandial glycaemia (PPG) as the mean value from the three following measurements of fasting glycaemia and measurements of glycaemia 2 hours after breakfast, lunch and dinner in the self-monitoring of blood glucose. The glomerular filtration rate (GFR) was calculated according to the Modification of Diet in Renal Disease Study Equation (MDRD).

Smoking status

Smoking status was self reported in questionnaire as current smoker, ex-smoker or never-smoker. We determined data about smoking status for 100% of the analyzed group. Patients were classified as smokers if they smoked one or more cigarettes daily at the time of follow-up and as ex-smokers if they had smoked in the past. Patients were asked also the time when they had started and, if they were ex-smokers, stopped smoking. Because the group of ex-smokers was very small (9 patients), all of them were heavy smokers for around 10 years and the mean time without smoking was less than 8 years we decided to divide patients into two groups of non-smokers and smokers (current and ex-smokers). Lifetime consumption was estimated in pack-years. The clinical characteristics of the two study groups are shown in Table 1.

Insulin resistance assessment

We assessed indirect parameters of insulin resistance, such as the body mass index (BMI), waist

Table 1. Clinical characteristics of patients according to smoking status [data are means ± SD, median (IQR) or n (%)]. The t-student test or Mann–Whitney test and Fisher's test or the Chi^2 test

	Ever-smokers	Non-smokers	p
Sex M/F	29/7	22/23	0.003
Age (years)	34.0 (31.0–41.5)	32.0 (29.0–36.0)	0.055
Duration of diabetes (years)	10.0 (9.0–11.0)	10.0 (9.0–11.0)	0.59
Hypertension n (%)	15 (19)	4 (5)	0.001
Weight [kg]	80.3 ± 14.4	72.9 ± 15.0	0.02
BMI [kg/m^2]	25.5 ± 3.7	24.1 ± 3.9	0.12
Waist circumference	89.6 ± 10.4	83.1 ± 10.9	0.007
Waist circumference (male)	86.2 ± 10.9	86.3 ± 10.8	0.058
Waist circumference (female)	86.4 ± 10.9	86.0 ± 10.9	0.94
WHR (waist-to-hip rato)	0.9 ± 0.08	0.86 ± 0.09	0.03
WHR (male)	0.88 ± 0.08	0.87 ± 0.08	0.03
WHR (female)	0.88 ± 0.08	0.87 ± 0.08	0.33
Daily insulin requirement [U/kg/d]	0.67 ± 0.16	0.67 ± 0.21	0.96
eGDR [mg/kg/min]	7.1 ± 2.5	8.8 ± 1.8	0.0005
eGDR < 7.5 n (%)	20 (55.6)	9 (20)	0.002
Metabolic syndrome n (%)	11 (30.5)	5 (11.1)	0.03
Systolic blood pressure [mm Hg]	120.0 (110.0–132.5)	120.0 (105.0–120.0)	0.03
Diastolic blood pressure [mm Hg]	80.0 (70.0–85.0)	75.0 (60.0–80.0)	0.08
FPG [mmol/l]	8.7 (7.0–11.1)	8.6 (6.4–11.1)	0.87
PPG [mmol/l]	9.1 (7.7–10.0)	8.8 (7.6–9.7)	0.29
HbA_{1c} (%)	8.47 ± 1.51	8.22 ± 1.6	0.48
HbA_{1c} (mean from years 1999–2007) (%)	8.43 ± 1.46	7.97 ± 1.39	0.16
TCH [mmol/l]	4.85 ± 0.76	4.6 ± 1.1	0.34
TG [mmol/l]	1.0 (0.8–1.5)	0.9 (0.6–1.2)	0.08
LDL-cholesterol [mmol/l]	3.0 (2.4–3.5)	2.5 (2.2–3.3)	0.12
HDL-cholesterol [mmol/l]	1.66 ± 0.40	1.69 ± 0.37	0.63
ALT [U/l]	19.0 (16.0–23.0)	16.0 (12.0–24.0)	0.13
AST [U/l]	18.5 (15.0–23.5)	17.0 (15.0–22.0)	0.49
GGTP [U/l]	23.0 (15.0–36.0)	15.0 (11.0–21.0)	0.003
GFR (MDRD) [ml/min/1.73 m^2]	110.5 (100.2–122.8)	107.1 (98.3–118.9)	0.77

ALT — alanine aminotransferase; AST — aspartate aminotransferase; BMI — body mass index; eGDR — estimated glucose disposal rate; FPG — fasting plasma glucose; GGTP — gamma-glutamyl transferase; GFR — glomerular filtration rate; high density lipoproteins (HDL) cholesterol, low density lipoproteins (LDL) cholesterol; PPG — postprandial plasma glucose; TCH — total cholesterol; TG — triglycerides; WHR — waist to hip ratio

circumference, waist-to-hip ratio (WHR), daily insulin requirement, estimated glucose disposal rate (eGDR) according to Williams [2] and the presence of features of metabolic syndrome. 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 from the following equation: BMI = weight (kg)/squared height (m^2) and WHR = waist circumference (cm)/hip circumference (cm). The patient's insulin requirement was expressed in units of total daily insulin dose (U) per kilogram body weight (kg). The estimated glucose disposal rate-eGDR was calculated according to the formula: 24.31 – (12.22 × WHR) – (3.29 × arterial hypertension 0/1) – (0.57 × HbA_{1c}), where the units are mg/kg/min [1, 2]. The value of the cut-off point was 7.5 mg/kg/min; patients with eGDR below 7.5 mg/kg/min were assumed to be insulin resistant, according to the clamp technique of DeFronzo [15].

Statistical analysis

The statistical analysis was performed using the STATISTICA 10.0 program. All data are expressed as means and standard deviations (± SD), as median values and interquartile ranges (IQR) and as numbers (percentage) of subjects. The patients were divided

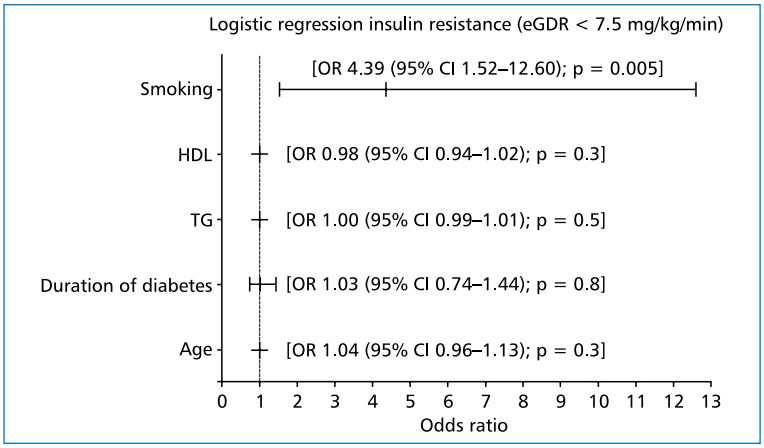

Figure 1. The results of a logistic regression model: the odds ratio [OR (95% confidence interval-CI)] for insulin resistance (estimated glucose disposal rate-eGDR < 7.5 mg/kg/min), adjusted for age, duration of diabetes, triglycerids (TG) and high density lipoproteins (HDL) cholesterol level

into two groups, according to the smoking status. The Mann–Whitney or t-Student's tests were used for continuous variables, and categorical variables using Fisher's test or the Chi^2 test were used to assess differences between groups of smokers and non-smokers. Normality of the data distributions was tested using Kolomogorow–Smirnov's test with Lilliefors correction. The backward logistic regression model was used to estimate the odds ratio (OR) for insulin resistance assessed with eGDR < 7.5 mg/kg/min, adjusted for age, duration of diabetes, TG and HDL-cholesterol levels. Because eGDR is calculated using HbA_{1c} and WHR values and presence or absence of arterial hypertension we didn't use this data in the regression model. Differences with a probability value < 0.05 were considered statistically significant.

Results

After approximately a 10-year follow-up, 45 (55.6%) patients never smoked cigarettes and 36 (44.4%) were smokers (27 current smokers and 9 ex-smokers). Among smokers 29 were man (80.5%). The prevalence of smoking in man was 56.8% and 23.3% in women. Mean lifetime consumption was 3734.9 ± 2411.6 pack-years. Insulin resistance, assessed with eGDR < 7.5 mg/kg/min, was stated in 29 patients (35.8%).

Patients who smoke or had ever smoked, compared with subjects who never smoked, were more often men (80.5% *vs.* 49%, p = 0.003) and had higher weight (80.4 ± 14.4 *vs.* 72.9 ± 15 kg, p = 0.02), larger waist circumference (89.6 ± 10.5 *vs.* 83.1 ± 10.9 cm, p = 0.003), higher WHR (0.9 ± 0.08 *vs.* 0.86 ± 0.09, p = 0.006) and systolic blood pressure [120 (110–132) *vs.* 120 (105–120) mm Hg, p = 0.03], higher level of GGTP [23 (15–36) *vs.* 15 (11–21) U/l, p = 0.003] and lower eGDR (7.11 ± 2.47 *vs.* 8.82 ± 1.79 mg/kg/min, p = 0.001) (Tab. 1).

A significant relationship, adjusted for age, duration of diabetes, TG and HDL cholesterol level, between smoking and eGDR < 7.5 mg/kg/min was revealed [odds ratio OR 4.39 (95% confidence interval CI 1.52–12.66); p = 0.005] (Fig. 1).

Discussion

Our results have clearly shown that smoking is independently associated with insulin resistance in patients with DM1. Insulin resistance influences management of DM1 and increases the risk of its chronic complications [1, 16]. The relationship of smoking with insulin resistance was described in patients with type 2 diabetes [13] and without diabetes [14]. Data about the relationship of smoking with IR among DM1 patients are not numerous and there are no previous publications about the association of smoking with indirect markers of insulin resistance in this group of patients. Thus, identifying the risk factors of IR in patients with DM1 seems very important.

The gold standard for determining insulin sensitivity in this group of patients is the euglycaemic insulin clamp technique of DeFronzo [15]. However, this technique is too complicated and expensive for clinical practice. We decided to evaluate insulin resistance by calculating eGDR. Estimated GDR was created by the authors of the Pittsburgh Epidemiology of Diabetes Complications Study. Wiliams et al. made a validation of a score based on clinical factors, correlated with the results of clamp, to determine the extent of insulin resistance in type 1 diabetes [2]. This marker of IR was used in randomized studies with type 1 diabetic patients such

as Diabetes Control and Complications Trial and Pittsburgh Epidemiology of Diabetes Complications Study. Estimated GDR in these studies was used to assess the relationship of IR with chronic diabetic complications [1, 17]. In our study insulin resistance evaluated with eGDR was present in 29 (36%) of patients. We have revealed significant, independent relationship between smoking and eGDR in patients with DM1. In the study of Attvall et al. using euglycaemic clamp technique, healthy habitual smokers had significantly reduced total glucose disposal during smoking in comparison to the results in non-smokers [18]. In patients with type 2 diabetes who smoke cigarettes GDR during euglycemic hyperinsulinemic clamp was around 45% lower than in non-smokers [13]. According to our knowledge this study is the first one evaluating the association of smoking status with indirect parameters of insulin resistance, such as eGDR, in patients with type DM1.

Moreover, we have evaluated in this group other indirect parameters of IR such as anthropometric data, lipid profile, liver function and the presence of metabolic syndrome. The DM1 patients who were smokers in the study group had features characteristic for insulin resistance syndrome. Firstly, they had higher WHR and waist circumference, factors which indicate abdominal obesity. In the National Heart, Lung and Blood Institute's Twin Study 265 pairs of identical twins were examined, what allowed eliminating influence of genetic factors. Authors revealed that WHR and waist circumference were strongly related with cigarette smoking [19]. Among obese people smokers had larger waist circumference than non-smokers [20, 21]. Secondly, in our study smokers had higher levels of systolic blood pressure and more often diagnosed hypertension than non-smokers. Smoking induces higher blood pressure levels in healthy men. Frati et al. reveled a significant elevation of blood pressure values while smoking [21]. However epidemiological studies have clearly shown that long term influence of smoking on blood pressure was substantial [22]. Moreover, the group of smokers had significantly higher serum GGTP levels, but within the normal range. Raised hepatic enzymes can be a markers of visceral fat, hepatic steatosis and hepatic insulin resistance. In the Data from an Epidemiological Study on the Insulin Resistance Syndrome (D.E.S.I.R.) GGTP was related to increased risk of metabolic syndrome, according to IDF definition, what was associated with insulin resistance, evaluated with HOMA index [23]. In more than 10.000 healthy persons smoking was positively associated with GGTP and HOMA-IR. Moreover, GGTP was related to a number of cigarettes smoked [24].

There are several mechanisms that could explain the pathophysiological relations between smoking and the development of insulin resistance. Firstly, smoking induces increased secretion of insulin-counter regulatory hormones such as cortisol, growth hormone and catecholamines [18, 25]. Secondly, it activates the sympathetic nervous system and stimulates the production of endothelin. Thus, smoking may reduce capillary flow and cause hypoxia [9, 22, 23]. Finally, modifications of some enzymes' activity, which take part in lipid metabolism, and increased lipolysis can result in elevated levels of free fatty acids. Nicotine and carbon monoxide may decrease lipoprotein lipase activity and increase 3-hydroxy-3-methylglutaryl-CoA reductase activity and glucose-3-phosphatase dehydrogenase activity [28, 29]. Those mechanisms are responsible for i.e. accumulation of fat in the muscles what induce IR in type 1 diabetic patients [8]. Moreover, free fatty acids directly disturb insulin signaling path [6]. Bergman et al. investigating influence of smoking on intramuscular lipid metabolism demonstrated that not concentration of intramuscular TG but its increased saturation may be combined with insulin action. Moreover, they observed increased insulin receptor substrate-1 Ser^{636} phosphorylation in smokers than in non-smokers that inhibits insulin signaling [30].

In summary, type 1 diabetic patients who smoke or ever smoked are more insulin resistant. Indirect parameters of insulin resistance, especially eGDR, and others such as WC, WHR and GGTP activity, have seemed to be helpful in diagnosis of insulin resistance in clinical practice. We would like to underline that these results could be of special importance because there is no data about the relationship of smoking with indirect parameters of IR in DM1. Moreover, this was a unique group of patients equally educated at baseline and treated with intensive insulin therapy from the onset of the disease. As smoking is a modifiable factor we can do much more in prevention of chronic complications. Clinicians have to evaluate the smoking status of their patients and try to promote smoking cessation. The risk of diabetic angiopathy can be reduced by adding interventions decreasing insulin resistance to smoking cessation.

Conclusions

The results of this study confirm the healthy dimension of not smoking among people with type 1 diabetes. Smoking in patients with type 1 diabetes, treated from the initial diagnosis with intensive insulin therapy, is associated with insulin resistance.

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Conflict of interest

Authors report no competing interests'.

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