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Smoking and development of type 2 diabetes in patients with decreased functional capacity

Alexander Tenenbaum[a,c,*], Enrique Z. Fisman[a,c], Yehuda Adler[a,c], Michael Motro[a,c], Valentina Boyko[b], Solomon Behar[b,c]

[a]*Cardiac Rehabilitation Institute, Chaim Sheba Medical Center, Tel-Hashomer, Israel*
[b]*Bezafibrate Infarction Prevention Study Coordinating Center, Neufeld Cardiac Research Institute, Chaim Sheba Medical Center, Tel-Hashomer, Israel*
[c]*Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel*

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Abstract

Objective: Data regarding the possible contribution of cigarette smoking to development of type 2 diabetes are scarce and inconclusive. Patients with impaired functional capacity and diminished physical activity are prone to develop new diabetes. However, the role of smoking on diabetes incidence among these patients has not been specifically investigated. The present study was aimed to evaluate the association between cigarette smoking and development of type 2 diabetes in patients with coronary artery disease and decreased functional capacity over a 6.2-year follow-up period.

Methods: The study sample comprised 630 nondiabetic patients aged 45–74 years, with a fasting blood glucose of <126 mg/dl and with impaired functional capacity (New York Heart Association functional class II and III). The sample was classified into two groups: 1) non smokers (never and past smokers pooled together)—552 patients and 2) current smokers—78 patients.

Results: Smokers were younger but they had a relatively unfavorable lipid profile (with respect to apolipoproteins A, triglyceride and HDL-cholesterol levels). No significant differences between the groups were found for weight, body mass index, total cholesterol and blood pressure. During the follow-up, development of new diabetes was recorded in 98 patients: in 80 (14.5%) non smokers and in 18 (23.1%) smokers, p=0.05. Among the non smokers, there were no significant differences in diabetes incidence between 357 past smokers and 195 never smokers: respectively, 48 (13.4%) and 32 (16.4%), p=0.34. In addition, all-cause mortality among the smokers (23.1%) was significantly higher than in non smokers (12.7%), p=0.01. Multivariate analysis identified current smoking as an independent predictor of increased risk of new diabetes development with a hazard ratio of 1.94 (95% confidence interval 1.16–3.25).

Conclusions: Current smoking was associated with an independent two-fold increased risk for development of type 2 diabetes in patients with impaired functional capacity.

Keywords: Coronary artery disease; Diabetes mellitus; Functional capacity; Smoking

The prevalence of type 2 diabetes continues to expand worldwide [1–6]. Physical inactivity, decreased functional capacity, increased body mass index, preexisting glucose and insulin abnormalities, advanced age and parental diabetes appear to be acknowledged factors associated with the development of new diabetes [7–10]. Both diabetes and smoking are well recognized major risk factors for accelerated atherosclerosis and coronary artery disease (CAD) [11]. However, data regarding the possible contribution of cigarette smoking to development of type 2 diabetes itself are scarce and inconclusive [12–16]. A number of recent reports have demonstrated that patients

* Corresponding author. Cardiac Rehabilitation Institute, Chaim Sheba Medical Center, Tel-Hashomer 52621, Israel. Tel.: +972 3 5302578; fax: +972 3 5303084.
E-mail address: altenen@post.tau.ac.il (A. Tenenbaum).

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with impaired functional capacity and diminished physical activity level are prone to develop new diabetes [17–20]. However, the possible role of smoking on the diabetes incidence in this high-risk group of patients with decreased functional capacity has not been specifically investigated.

The present study was aimed to evaluate the possible association between cigarette smoking and development of type 2 diabetes in patients with coronary artery disease and decreased functional capacity, who participated in the Bezafibrate Infarction Prevention (BIP) study, over a 6.2-year follow-up period.

1. Methods

1.1. Subjects

The major inclusion and exclusion criteria for the BIP study, as well as the ethical guidelines, have been previously reported [21]. In brief, inclusion criteria for men and women comprised: age 45–74 years, history of myocardial infarction no less than 6 months and not more than 5 years prior to enrollment in the study and/or stable angina pectoris confirmed by coronary angiography, and/or radio–nuclear studies or standard exercise tests.

The major exclusion criteria for the BIP study were: permanent pacemaker implantation, cerebrovascular disease, chronic hepatic or renal disease, peripheral vascular disease, malignant diseases, estrogen replacement therapy, insulin-dependent diabetes mellitus and current use of a lipid modifying drug.

After an initial 2 months of a lipid-lowering diet, there were 3122 eligible patients who were included in the BIP study between May 1990 and January 1993. There was no difference in the distribution of all-cause and cardiac mortality between the bezafibrate and placebo study groups [22].

Functional capacity classes were evaluated by certified cardiologists, according to the New York Heart Association (NYHA) classification [23], following thorough clinical examinations in the framework of university-affiliated hospital cardiology departments. Decreased functional capacity was defined as the presence *on baseline* of NYHA functional class ≥II.

Among the BIP study patients there were 311 diagnosed diabetics, 141 patients with a fasting blood glucose level of ≥126 mg/dl (7 mmol/l) (undiagnosed diabetics), 1986 patients with a normal functional capacity (NYHA functional class I) and 54 patients with unknown glucose metabolism or functional status: all these patients were excluded from this analysis. Thus, the final study sample for this post-hoc analysis comprised 630 nondiabetic patients with impaired functional capacity (NYHA II—518 and NYHA III—112 patients). In accordance with the ADA classification [24], we defined the detection of a fasting blood glucose level ≥126 md/dl (7 mmol/L) during the follow-up period as the criterion for new diabetes.

Routine visits to the clinics were scheduled bimonthly for study medication distribution and compliance assessment by tablet count, every 4 months for clinical evaluation, and every year for blood analyses.

The study was a multicenter prospective trial, performed in 18 university-affiliated hospitals. The follow-up period lasted until January 1999 (mean 7.7±0.8, range 6–9 years).

1.2. Laboratory methods

Detailed data on laboratory methods were given in a previous report [22]. Briefly, blood samples, collected in the 18 participating medical centers using standardized equipment and procedures, were transferred in cooled containers, to a central laboratory. Blood samples were drawn after at least 12 h of fasting, for determination of serum levels of cholesterol, HDL-cholesterol and triglycerides. Laboratory measurements were carried out using standard automated procedures with commercially available kits (Roche Diagnostics). Fasting blood glucose values were determined by the GOD-PAPP method, employing a BM/Hitachi 717/911 analyzer [22].

Plasma insulin was estimated by routine radio immunoassay (Insik 5; Sorin Biomedica, Saluggia, Italy). The homeostatic indexes of insulin resistance (HOMA IR and QUICKI) were calculated according to the homeostasis model of assessment as follows [25–27]:

HOMA IR = fasting insulin (μU/ml) * fasting glucose (mmol/l) / 22.5; and

QUICKI = 1 / [log fasting insulin (μU/ml) + log fasting glucose (mg/100ml).

1.3. Determination of additional variables

Criteria for the diagnosis of myocardial infarction, anginal syndrome, hypertension and congestive heart failure have been previously reported [22]. Briefly, the diagnosis of ischemic heart disease was made in patients with documented myocardial infarction or typical angina pectoris in whom there was also a positive exercise test, evidence of myocardial ischemia revealed by radionuclide studies or at least 60% stenosis of one major coronary artery.

Smoking habits (357 past smokers, 195 never smokers, and 78 current smokers) were determined on the basis of self-reporting by the patients during interviews held with study physicians. Since never smokers and past smokers were very similar in regard to their baseline and follow-up characteristics, they were pooled together and definded as non smokers. Current smokers reported about the number of cigarettes smoked per day and the duration of smoking in years. A pack-year was defined as smoking 20 cigarettes/d for 1 year. Current smokers were subdivided into three subgroups in accordance with the number of pack-years: up

to 20.0 pack-years (31 patients), >20 pack-years (33 patients), and unknown number of pack-years (14 patients).

1.4. Statistical analysis

Data were analyzed using the SAS software [28]. Continuous variables were presented as mean values ± standard deviation (SD). Comparisons between groups were made using the chi-square test for discrete variables and *t*-test for continuous variables. Kaplan–Meier curves were produced using the LIFETEST procedure [29]. The log–rank test was used for comparing the curves.

Multivariate analysis of incidence of new diabetes was performed using the Cox proportional hazard model with stepwise selection (PHREG procedure) to account for different lengths of follow-up and correlation with covariates [29]. The significance levels for entering and removing an explanatory variable were set at 0.15 and 0.10. Variables included in the model were age, gender, presence of NYHA III functional class, total cholesterol, triglycerides, glucose, hypertension, previous myocardial infarction, peripheral vascular disease, anginal syndrome, chronic obstructive pulmonary disease (COPD), bezafibrate treatment and body mass index.

2. Results

Our population included 2 groups: 1) non smokers (never and past smokers pooled together)—552 patients, and 2) current smokers—78 patients.

2.1. Baseline data

The main clinical and laboratory characteristics of patients are presented in Table 1. The majority of the patients in all groups were men (among smokers there were significantly less women) and had sustained a myocardial infarction in the past. Smokers were younger and their baseline fasting glucose level was somewhat lower. However, the prevalence of COPD was higher in smokers and they had relatively unfavorable lipid profiles (with respect to apolipoproteins A, triglyceride and HDL-cholesterol levels). No significant differences between the groups were found for weight, body mass index, total cholesterol and blood pressure.

The fasting insulin level and indexes of insulin sensitivity (HOMA IR and QUICKI) were determined in 175 study patients: in 152 (28%) non smokers and in 23 (29%) smokers. No significant differences between the groups were found for these parameters: fasting insulin level—11.3±5.7 μU/ml non smokers vs 10.8±5.0 μU/ml in smokers (p=0.7); HOMA—2.8±1.7 in non smokers vs 2.6±1.2 in smokers (p=0.5); and QUICKI—0.34±0.03 in smokers vs 0.342±0.02 smokers (p=0.99).

Table 1
Baseline characteristics of the study population

Characteristics	Non smokers (n=552)	Smokers (n=78)	p value
Age (years)	60.9±6.3	58.9±6.7	0.009
Body mass index (kg/m^2)	27.1±3.5	27.3±3.3	0.5
Women (%)	65 (12)	3 (4)	0.03
Past myocardial infarction (%)	389 (71)	58 (74)	0.5
Angina (%)	488 (88)	70 (90)	0.7
Hypertension (%)	189 (34)	24 (31)	0.5
COPD (%)	13 (2.4)	9 (12)	<0.001
Systolic blood pressure (mm Hg)	133±18	133±18	0.8
Diastolic blood pressure (mm Hg)	80±9	80±8	0.7
Heart rate (beats/min)	70.4±10	72.6±9.7	0.06
Glucose* (mg/dl)	97.1±11	95.9±13	0.4
Total cholesterol (mg/dl)	213±18	212±20	0.7
HDL-cholesterol (mg/dl)	34.5±5.4	33.0±5.3	0.02
LDL-cholesterol (mg/dl)	149±17	148±18	0.5
Triglycerides (mg/dl)	145±53	156±56	0.09
APO A (mg/dl)	101±13	97±13	0.003
APO B (mg/dl)	101±12	102±14	0.9

HDL, LDL—high and low density lipoproteins; *—fasting level; Apo A and B—apolipoproteins A and B; and COPD—chronic obstructive pulmonary disease. Data are mean±SD or number (%) of patients.

Data regarding treatment with cardiovascular drugs among the study groups are presented in Table 2. At baseline, nitrates, calcium antagonists, beta blockers and antiplatelet drugs (mainly aspirin) were the most commonly used medications. More non smokers received diuretics than their counterparts. The use of the angiotensin-converting enzyme inhibitors, especially among the smokers, was low. There were no significant differences in the proportion of patients receiving the other cardiovascular drugs.

2.2. Changes in fasting blood glucose level during follow-up

In total, mean level of fasting blood glucose increased significantly during follow-up among all study groups (Fig. 1), but the magnitude of change in smokers was greater than in non smokers: the mean change in non smokers was 2.7–23.1 [last vs first visit, paired *t*-test p=0.007] and the mean change in smokers was 8.2–24.9, p=0.006.

2.3. Development of new diabetes and other main outcomes

Per definition, there were no patients with diabetes among the study groups at the beginning of the follow-up. Patients were followed from 4.6 to 7.6 years (mean follow-up period 6.2 years). During this period, development of new diabetes was recorded in 98 patients: in 80 (14.5%) of non smokers and in 18 (23.1%) of smokers, (p=0.05). Among the non smokers, there were no significant differences in the diabetic incidence between 357 past smokers and 195 never smokers: respectively, 48 (13.4%) and 32

Table 2
Distribution of cardiovascular drugs among the study patients

Drugs	Non smokers (n=552)	Smokers (n=78)	p value
Beta blockers (%)	234 (42)	28 (36)	0.3
Nitrates (%)	365 (66)	50 (64)	0.7
Calcium antagonists (%)	349 (63)	45 (58)	0.3
Diuretics (%)	125 (23)	9 (12)	0.02
Antiplatelets (%)	361 (65)	43 (55)	0.08
Angiotensin converting enzyme inhibitors (%)	94 (17)	5 (6.4)	0.02

(16.4%), p=0.34. Among the smokers there were 31 patients with 1–20 pack-years history (diabetic incidence 19.4%), 33 patients with >20 pack-years history (diabetic incidence 30.3%) and 14 patients with unknown pack-years history (diabetic incidence 14.3%), p=0.4.

In addition to increasing the incidence of disease, the mean time until onset of new diabetes was significantly reduced in smokers in comparison with non smokers: 59–26 vs 65–22 months, p=0.02 (mean acceleration was approximately half of a year).

All patients in whom diabetes was diagnosed during the study were initially on diet. In addition, 35 (36%) patients with new diabetes received oral antihyperglycemic drugs afterwards.

Kaplan–Meier curves of diabetes incidence (in accordance with the time of diagnosis following annual fasting blood glucose level measurements) for the study groups are presented in Fig. 2. The higher incidence rate was observed for the smokers (p Plog-rank=0.03).

In regard to clinical outcomes, we found a significantly higher all-cause and non cardiac mortality among the smokers (Table 3). The cardiac mortality of the smokers tended also to be higher than in the non smokers, but this tendency did not reach statistical significance.

Multivariate analysis with adjustment for significant variables identified current smoking as an independent predictor of increased risk of new diabetes development

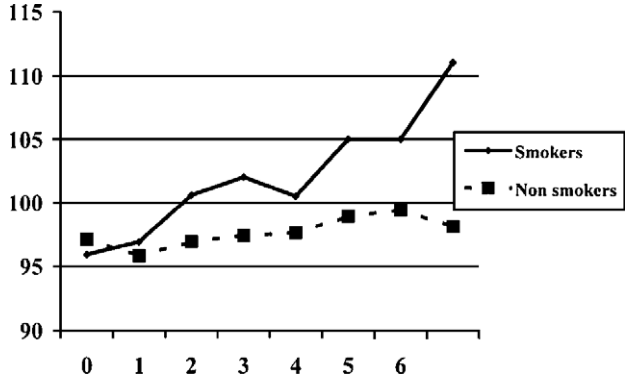

Fig. 1. Changes in mean fasting blood glucose (vertical axis, mg/dl) values throughout the study period (horizontal axis, years), following annual measurements (non smokers vs smokers). Each data point represents the mean value for all participants who remained at that time.

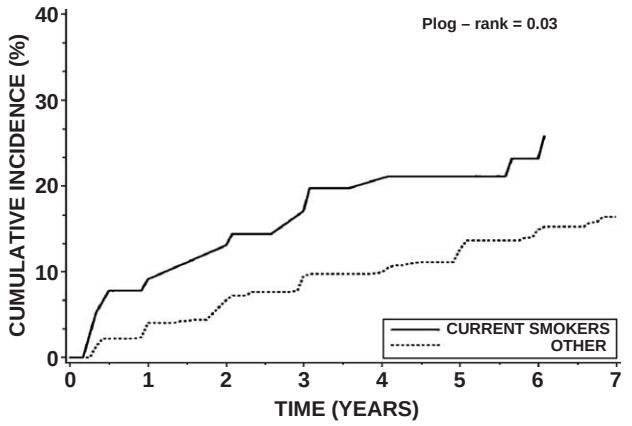

Fig. 2. Kaplan–Meier curves of diabetes incidence (in accordance with the time of diagnosis following annual fasting blood glucose measurements) for the study groups (non smokers vs smokers).

with a hazard ratio (HR) of 1.94 [95% confidence interval (CI) 1.16–3.25].

Other significant variables associated with future diabetes manifestation were baseline fasting glucose (10 mg/dl increment) with a HR of 2.4 (95% CI 1.96–2.93) and body mass index (1 kg/m^2 increment) with a HR of 1.09 (95% CI 1.04–1.15).

3. Discussion

We found that current smoking was associated with an independent two-fold increased risk for development of type 2 diabetes in patients with impaired functional capacity. In addition, smokers were younger than non smokers, but their all-cause mortality was significantly higher. It is possible, that due to increased risk of early mortality among smokers part of them did not reach this study end-point (development of type 2 diabetes). Therefore, the true contribution of smoking on diabetes incidence may be underestimated in our study. Analyses of risk for type 2 diabetes according to pack-years revealed a dose-dependent tendency, although it did not reach statistical significance due to insufficient statistical power of our study for subgroup analysis.

Being a past smoker was associated with the same or even with a non significantly lower risk for type 2 diabetes compared with never smokers. These data strongly support

Table 3
Main outcome of the study population during follow-up

Characteristics	Non smokers (n=552)	Smokers (n=78)	p value
New diabetes (%)	80 (14.5)	18 (23.1)	0.05
Total death (%)	70 (12.7)	18 (23.1)	0.01
Cardiac death (%)	44 (8.0)	12 (10.3)	0.5
Non-cardiac death (%)	26 (4.7)	10 (12.8)	0.004
Primary endpoint* (%)	80 (14.5)	15 (19.2)	0.3

* The primary endpoint of the BIP study was fatal or non-fatal myocardial infarction or sudden death.

an overwhelming importance of smoking cessation in the framework of secondary prevention policy in patients with decreased functional capacity. On the other hand, the relationship between smoking and type 2 diabetes may be much more complex. Smoking cessation commonly results in weight gain, which increases the risk for diabetes [30]. We also demonstrated that body mass index was independently associated with future diabetes manifestation. Our data agree with previous studies [12,31] in which the relative risk for diabetes associated with cigarette smoking was stronger in leaner than in obese patients. Furthermore, in a recent experimental study [32], long-term oral nicotine administration reduced insulin resistance in obese diabetic rats and contributed to lowering of blood glucose levels. These results emphasized the crucial component in smoking cessation management: we need not only promote smoking termination but also concomitantly help patients avoid weight gain.

Evidence is increasing that in some populations, type 2 diabetes shares common causal factors with CAD [16,33]. Patients with CAD and impaired functional capacity usually diminished their exercise activity with more positive energy balance. An inverse relationship between physical activity level and the risk of subsequent type 2 diabetes has been described [34–36]. Therefore, the thesis that patients with impaired functional capacity are prone to develop new diabetes seems to be based on a reliable theoretic background and has been stressed in previous reports [17–20].

To the best of our knowledge, this study is the first one which evaluates the development of new diabetes in patients with impaired functional capacity in accordance with their smoking habits. The mechanism of how cigarette smoking increases the risk for type 2 diabetes remains to be elucidated. In our opinion, there are three major possible explanations for this observation: 1) Previous studies have indicated that cigarette smoking may cause insulin resistance in peripheral tissues and hyperinsulinemia [37–39]. Currently, an insulin-resistant state constitutes the major risk factor for the development of diabetes mellitus [40,41]. People who develop type 2 diabetes usually pass through the phases of insulin resistance, hyperinsulinemia, pancreatic beta cells stress and damage leading to progressively decreasing insulin secretion, elevated glucose postprandial and fasting levels; 2) Recently, the concept of oxidative stress has been introduced as a unifying pathological mechanism for atherogenesis and pancreatic beta cells stress and damage leading to type 2 diabetes [42–45]. Oxidative stress is caused by a variety of stimuli, including cigarette smoking [44,45]; and 3) Chronic inflammation may also be a risk factor for developing type 2 diabetes [46–50]. Cigarette smoking itself causes airway inflammation in smokers and the correlation between level of hematologic markers of inflammation and smoking intensity has been reported [45,51,52].

The Diabetes Prevention Program (DPP) results have shown that individualised, systematic and intensive lifestyle interventions (including dietary changes, increased physical activity and weight loss) are the most effective means of prevention of type 2 diabetes in high risk populations [53]. There are limited data regarding prevention of type 2 diabetes by pharmacological interventions [54–56]. Our data provide new evidence that cigarette smoking is an additional important modifiable risk factor that could be targeted for prevention of diabetes. Stressing the point that smoking increases the risk of diabetes development may convince more smokers to quit.

4. Conclusions

Current smoking was associated with an independent two-fold increased risk for development of type 2 diabetes in patients with impaired functional capacity over a 6.2 year follow-up period.

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