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ORIGINAL ARTICLE

Impact of smoking on progression of vascular diseases and patient survival in type-1 diabetic patients after simultaneous kidney–pancreas transplantation in a single centre

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Summary

We evaluated the impact of smoking on the progression of macro-angiopathy as well as patient and graft survival in 35 type-1 diabetic patients with simultaneous kidney–pancreas transplantation (SKPT). According to their smoking history, the patients were divided into smokers ($n = 12$) and nonsmokers ($n = 23$). Mean observation period was 80 (12–168) vs. 84 (12–228) months. The prevalence of vascular diseases as well as the incidence of vascular complications during the observation period was evaluated in each group. Graft- and patient survival were calculated. The prevalence of all vascular diseases was higher in the smokers with prior SKPT at the start as also at the end of study; however, the differences were not significant. In addition, the incidence of vascular complications (stroke, myocardial infarction and amputation) during the follow-up period was higher in the smoking group. Taking all vascular complications together (events/patient/year) the difference was significant (0.105 vs. 0.066, $P < 0.05$). One- and 5-year patient survival was 100% and 75% for smokers vs. 100% and 91% for nonsmokers. One- and 5-year pancreas graft survival at the same time was 100% and 75% in living smokers as well as 100% and 83% in the nonsmokers: We conclude that smoking after SKPT is associated with a progression of macro-angiopathy. Additionally, mortality after SKPT tends to be higher in smoking patients.

Introduction

Simultaneous kidney–pancreas transplantation (SKPT) is accepted as the therapy of choice in type-1 diabetic patients with end-stage renal disease (ESRD) on account of diabetic nephropathy (DNP). Recent reports have demonstrated an improved cardiovascular outcome after SKPT compared with kidney transplantation alone (KTA) in type-1 diabetic patients [1–3] and in several studies it has been shown that the long-term patient survival is better after SKPT than after KTA [2,4,5].

Smoking in diabetic patients is associated with a very high mortality, especially, in female diabetic subjects an excess mortality was reported on account of a markedly excessive risk of coronary heart disease mortality in smokers [5,6]. The impact of smoking on renal disease is well known; in several studies, it has been shown that the progression of DNP is significantly increased in smokers [4,7,8]. In a recent study, smoking has been identified as a risk factor also for a limited kidney graft survival [8]. Thus, smoking is one of many well known modifiable factors, which are responsible for the limitation of

patient-and graft survival [8,9]. Additionally, in patients with a graft, immunosuppressive therapy may affect cardiovascular risk too [10].

There are no data in the literature concerning smoking as a risk factor in SKPT patients. In our study, the mainly excepted outcomes of this study were differences in vascular diseases as well as different patient- and graft survival after SKPT in patients with and without smoking. The hypothesis was that smokers will have poorer cardiovascular outcomes and worse graft survival when compared with nonsmokers. In the present study we evaluated the prevalence of vascular diseases prior to transplantation and at the end of the study, as well as the incidence of vascular complications during the observation period after SKPT in type-1 diabetic patients with and without smoking.

Thus, the aim of the study was to analyze the impact of smoking on the progression of macro-angiopathy as well as patient- and graft survival in SKPT patients.

Patients and methods

During the years I/1988–VI/2006, renal replacement therapy was started in our dialysis centre in 48 type-1 diabetic patients (C-peptide <0.2 ng/ml) who suffered from ESRD on account of DNP. All patients were already under control in our outpatient care unit for at least 2 years before the start of dialysis. Patients who died within 3 months after initiating dialysis were not registered for this study. Seven patients opted themselves for kidney transplantation and five patients were excluded from SPKT based on age and severe coronary disease. The other 36 patients received SKPT at the University Hospital, Innsbruck, in one case the pancreas graft was per-acutely rejected and immediately explanted during operation. Therefore, in respect of 35 type-1 diabetic patients both grafts were successfully transplanted and these patients were included in this retrospective study. The data were retrospectively evaluated, the determination of outcomes was done in a blinded fashion.

Patients were required to stop smoking before being listed for transplantation. SKPT was performed only when patients accepted that smoking was not permitted after transplantation. All patients were asked for details of their cigarette consumption before SKPT and 1 year after SKPT. All patients were routinely followed up at our outpatient care unit. Patients were divided into two groups, those with and without smoking. The end of the study was June 2006, the other end points of the study being death or ESRD.

We measured in intervals of 2 months in both groups the vascular risk factors blood pressure, cholesterol and triglycerides as well as serum creatinine (multi-channel Hitachi auto-analyzer; Hitachi, Roche, Vienna, Austria), HbA1c (Biorad company, Vienna, Austria) and creatinine clearance (Cr-Cl) calculated (Cockroft formula). In all patients, a 12-lead electrocardiogram (ECG), an echocardiography investigation and a doppler blood flow study of the carotid arteries and of peripheral arteries of the lower legs (Scanner with 7.4 MHz Ultramark 5 and 9; Advanced Technology Laboratories, Vienna, Austria) were performed prior to transplantation and subsequently as necessary. Additionally, a thallium scan was performed in 22 patients (63%) and/or a coronary angiography in 29 patients (83%) before SKPT. In a retrospective analysis the prevalence of vascular diseases was compared in the patient: cerebrovascular disease (CVD), coronary artery disease (CAD) and peripheral vascular disease (PVD) at the time of SKPT and at the end of the observation period. Moreover, we compared in both groups the incidence of severe vascular complications, defined as stroke, myocardial infarction and/or amputation of a leg, during the study period.

Two patients received a second kidney graft 2 and 7 years respectively after the first transplantation, and also two patients received a second pancreas graft seven and 8 years respectively after the first SKPT. In these cases, the graft function was defined as the first graft failure. During the last two decades, the surgical technique has been changed. In earlier years, the bladder was used to drain the exocrine pancreas secretion, in more recent years the enteric drainage became the preferred technique in most centres. During the same period, the routine immunosuppressive therapy has been changed, before 1996, cyclosporine combined with azathioprine was usually used for immunosuppressive therapy, since 1996, tacrolimus and mycophenolate mofetil (MMF) became the leading immunosuppressive drugs, later on completed by sirolimus and everolimus.

The CVD was defined as stroke stage III or IV in history, carotid artery stenosis or stricture by duplex sonography and/or carotid artery intervention. The diagnosis of CAD was based on myocardial infarction in history, angina pectoris and/or ischemic changes by ECG (ST deviation) in rest or during physical exercise, coronary artery stenosis by coronary angiography and/or intervention. The PVD was defined as mediasclerosis, ankle/brachial pressure index <0.7 with and without ischemic pains in the legs, and ischemic ulceration or necrosis requiring and/or an intervention in history. Intervention was defined as percutaneous transluminal angioplasty with/without stent implantation and/or artery bypass surgery. Renal grafts were considered as functioning as long as the patient did not require dialysis [Glomerulation filtrate rate (GFR) > 20 ml/min/1.73 m^2], and pancreas graft was considered functioning when no exogenous insulin was required. Finally, we wanted to

evaluate the causes of death during the post-transplant period.

Statistical analyses

For statistical analysis, the SPSS for Windows statistical program was used (SPSS Inc., Chicago, IL, USA). Statistical methods included the paired Student's *t*-test for comparing differences within the groups and the unpaired Student's *t*-test to compare data between the groups. For comparison of differences between groups with data not normally distributed the Wilcoxon and the Man–Whitney *U*-test as nonparametric statistic was used.

A *P*-value <0.05 was considered as statistically significant.

Results

According to their smoking history, we divided the patients in smokers ($n = 12$) and nonsmokers ($n = 23$). Smoking status was as defined according to the following: (i) nonsmokers: never smoked or quit >5 years prior to transplant. (ii) smokers: smoked at the time of transplant. Any patient smoking after transplant was considered as smoker regardless of their pretransplant status. We used the pack-years method, as described in the literature, to evaluate more exactly the cigarette exposure [9]: In the 12 patients, defined as smokers, the cigarette consumption varied between ½ pack and two packs per day, and in two patients ¼ pack daily. All patients were required to stop smoking before being listed for transplantation. Immediately and 6 months after transplantation the 12 smokers continued to stop cigarette smoking, however, 1 year after SKPT the patients resumed smoking but reduced their cigarette consumption to ¼–½ pack daily in seven cases, to ½–1 pack daily in four cases, and to 1/4 pack in one patient. In the 12 smokers the total number of pack-years was 20 (12–24) during the period before and after transplantation. In the 23 nonsmokers, 19 patients had never smoked and four patients had only a short exposure in history (<3 pack years) at least 5 years before SKPT. The mean duration of follow-up of the patients with functioning SKPT was 80 (12–168) months in the smoking group and 84 (12–228) months in the nonsmokers. The baseline data prior to transplantation and additionally the nonmodifiable risk vectors are shown in Table 1.

The modifiable vascular risk factors were similar in the groups with and without smoking, only the mean systolic blood pressure values were higher (smokers 136 ± 11 vs. 131 ± 13 mmHg, NS) as well the diastolic blood pressure (80 ± 5 vs. 79 ± 6 mmHg, NS). All risk factors in both groups (mean values of the observation period) are summarized in Table 2.

Table 1. Baseline data prior to transplantation and nonmodifiable vascular risk factors in the patients with and without smoking.

	Smokers ($n = 12$)	Nonsmokers ($n = 23$)
Baseline data		
Age (years)	43 ± 8	45 ± 7
Female (%)	50	48
BMI	23 ± 3	24 ± 4
HbA1c (%)	7.9 ± 1.8	7.2 ± 1.1
Nonmodifiable vascular risk factors		
Caucasian ethnicity (%)	100	100
Diabetes duration (years)	24 (18–36)	25 (18–38)
Dialysis duration (months)	9 (0–24)	7 (0–24)

Data given as mean ± SD or range and percentage (%).

Table 2. Modifiable vascular risk factors (mean values after transplantation during the observation period).

	Smokers	Nonsmokers
HbA1c (%)	5.6 ± 0.3	5.5 ± 0.3
Systolic blood pressure (mmHg)	136 ± 11	131 ± 13
Diastolic blood pressure (mmHg)	80 ± 5	79 ± 6
Antihypertensive drugs (*n*)	2 (0–3)	2 (0–4)
Angiotensin converting enzyme inhibitors (%)	33	30
Cholesterol (mg/dl)	219 ± 38	194 ± 43
Triglycerides (mg/dl)	146 ± 66	136 ± 66
Statine therapy (%)	36	30

Data given as mean ± SD or range, and percentage (%).

The prevalence of vascular diseases prior to SKPT and at the end of the observation period was higher in the smoking group; the prevalence of CAD was 42% before SKPT and 67% after transplantation versus 35% and 45% respectively in the group without smoking. In each group, the differences were not statistically significant; however, taken all vascular diseases together, the difference was significant ($P < 0.05$). The prevalence prior to SKPT was 1.2-fold higher in the smokers and at the end of the study 1.6-fold higher than in the nonsmokers. The per cent increase of the prevalence of vascular diseases was also higher in the smokers, for example for CAD 29 versus 59%, but differences were also not statistically significant. In addition, the incidence (events/patient/year) of vascular complications (stroke, myocardial infarction and/or amputations at the lower legs was higher in the smoking group. Comparing all vascular complications together the incidence was 1.6-fold higher in the smokers; the difference was also statistically significant with incidence of

Table 3. Prevalence of cerebrovascular disease (CVD), coronary artery disease (CAD) and peripheral vascular disease (PVD) prior to SKPT and at the end of the observation period as well per cent increase of prevalences and incidence of severe vascular complications (stroke, infarction and amputation) during the same period.

	Smokers	Nonsmokers
Prevalences of vascular diseases (%)		
Prior to SKPT		
CVD	33	26
CAD	42	35
PVD	42	26
End of study		
CVD	50	35
CAD	67	45
PVD	67	35
Per cent increase		
CVD	52	35
CAD	59	29
PAD	59	35
Incidence of vascular complications (*n*/patient/year)		
Stroke and/or intervention	0.035	0.018
Myocardial infarction and/or intervention	0.047	0.024
Amputation and/or intervention	0.035	0.024
Total incidence	0.105*	0.066*

SKPT, simultaneous kidney–pancreas transplantation.
*$P < 0.05$.

0.105 in the smokers and 0.066 in the nonsmokers ($P < 0.05$). These data are presented in Table 3. The prevalence of all vascular diseases is also demonstrated in Fig. 1. The incidence of vascular complications is shown in Fig. 2. The mean HbA1c levels were similar at the beginning as also at the end of the observation period.(VI/2006), in the same way, the kidney function remained stable during the same period, the decline of GFR was minimal, the Cr-Cl dropped from 66 + 11 to 64 + 15 ml/min/1.73 m^2 in the smoking group and from 66 + 11 to 62 + 16 ml/min/1.73 m^2 in the nonsmokers. These data are summarized in Table 4.

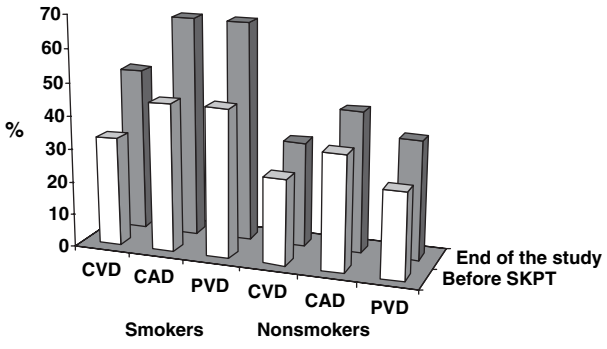

Figure 1 Prevalence (%) of cerebrovascular disease (CVD), coronary artery disease (CAD) and peripheral vascular disease (PVD) before (clear columns) and after the period of observation in patients with functioning pancreas graft (dark columns) in smoking and nonsmoking patients with simultaneous kidney–pancreas transplantation (SKPT).

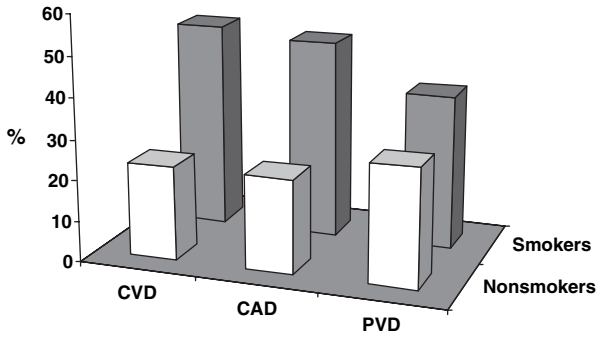

Figure 2 Percentual increase of prevalence of vascular diseases during the total observation period.

Table 4. Glycaemic control and graft function study including creatinine clearance (Cr-Cl) – 4 weeks after transplantation and at the end of the study.

	Smokers	Nonsmokers
Graft function 4 weeks after SKPT		
HbA1c (%)	5.5 ± 0.4	5.6 ± 0.3
Serum creatinine (μmol/ml)	105 ± 26	109 ± 30
Cr-Cl (ml/min/1.73 m^2)	69 ± 11	66 ± 10
Graft function at the end of study		
HbA1c (%)	5.6 ± 0.4	5.7 ± 0.5
Serum creatinie (μmol/ml)	138 ± 79	132 ± 69
Cr-Cl (ml/min/1.73 m^2)	61 ± 12	63 ± 13

SKPT, simultaneous kidney–pancreas transplantation.

The immunosuppressive therapy was similar in both groups: duration of steroid therapy was 6 (2–12) vs. 5 (1–12) months. During the main time of the observation period the smokers and nonsmokers received cyclosporine in 33% vs. 22%, tacrolimus in 64% vs. 77%, azathioprine 33% vs. 17% and MMF in 69% vs. 85%. These differences were not statistically significant.

Four patients in the smoking group died (33%) during the mean observation period of 80 months, during a similar period of 84 months only two nonsmoking patients died (9%). Therefore, the mortality rate (death/patient/year) during the observation period was 5% in the smoking group and 1.2% in the nonsmokers ($P < 0.05$). The 1-year patient survival was 100% in both groups. The 5-year patient survival was 75% in the smoking and 92% in the nonsmoking group. The 1-year pancreas graft survival was 100% in each group, the 5-year graft survival

was 75% in living smokers and 84% in the nonsmokers: The causes of death were sepsis ($n = 2$); tuberculosis ($n = 1$) and myocardial infarction ($n = 3$).

Discussion

In our study, smoking patients with SKPT were associated with a significantly higher prevalence of vascular diseases both before and after SKPT, as also during follow-up a significantly higher incidence of vascular complications were noted in comparison to the nonsmoking group.. In addition, the mortality in smokers was higher than that in nonsmoking patients (33% vs. 9% after a mean duration of approximately 7 years of well functioning pancreas transplant). Earlier studies demonstrated that smoking is a predictor of mortality in both, in the predialysis period as well as under haemodialysis [6,11]. Smoking cessation is demanded from each diabetic patient before the patients is accepted for SKPT.

In our study, 12 subjects were current smokers prior to transplantation. Immediately after SKPT all patients discontinued smoking. However, within 1 year after transplantation most of these patients smoked again, but cigarette consumption was lower than what used to be before transplantation. Obviously, smoking cessation in SKPT patients is only transiently successful in most cases. Therefore, for smoking transplant recipients: an anti-smoking program should be implemented [12]. In several studies, it was demonstrated that smoking is a high potent cardiovascular risk factor for patients after transplantation [9,12]. In our study, the prevalence of all vascular diseases prior to the SKPT was in the smokers 1.2-fold higher and at the end of study 1.6-fold higher than in the nonsmokers. Similarly, the incidence of vascular complications was 1.6-fold higher in the smoking patients ($P < 0.05$). The risk of modalities of renal replacement therapy, at any rate continues to be substantially higher than in the general population. Among the factors predicting patient- and graft survival are hypertension, dyslipidemia, and smoking, the most important factors [13,14]. Cigarette smoking is a major renal risk factor, which has not been sufficiently acknowledged despite increasing evidence [15]. Tobacco-use adversely affects transplant outcomes such as graft survival, patient survival, and other conditions that alter transplant patients' longevity. Particularly concerning the tobacco consumption's relationship to cardiovascular disease, the cardiovascular events are the most common cause of death in kidney transplant recipients [6,16] and it may be assumed that smoking is also a cardiovascular risk factor in pancreas graft recipients. Surprisingly, in our study, the causes of death were infections (50%) and cardiovascular events (50%). However, the vascular complications were significantly higher in our smoking group. Two of our patients died with functioning pancreas graft.

The endothelial and thrombotic effects of smoking are well known [13,17]. In a recent publication it was reported that long-term smoke exposure can result in systemic oxidants-antioxidants imbalance as reflected by increased products of lipid peroxidation and depleted levels of antioxidants like vitamins A and C in plasma of smokers. A low-grade systemic inflammatory response is evident in smokers as confirmed by numerous population-based studies: elevated levels of C-reactive protein (CRP), fibrinogen, and interleukin-6. Furthermore, rheological, coagulation and endothelial function markers like haematocrit are altered in chronic cigarette smokers [18]. In our study CRP was not measured in earlier years, however, data were available in most cases (10 smokers and 17 nonsmokers), the mean value was significantly higher in the smoking group (2.1 ± 0.8 vs. 0.9 ± 0.5 mg/dl, $P < 0.01$) Other causes for lower patient- and graft survival could be excluded. An elevated blood pressure is one of the main reasons for higher mortality and lower pancreas graft survival in the smoking patients. However, in our study the blood pressure was slightly higher in the smoking group, but not significantly. The lipid-levels were similar in smokers and nonsmokers. The surgery technique was similar. In the smoking group the bladder drainage was used in 42% compared to 26% in the nonsmokers, in whom enteric drainage was preferred in 72% vs. 58% in the smokers [19]; but difference was not significant. In addition, the smoking patients received SKPT more commonly (67%) prior to 1995, the nonsmokers were transplanted more frequently (61%) after 1995, the difference was not statistically significant: In addition, the immunosuppressive therapy was similar in both groups. Therefore, it may be assumed that an influence of the atherosclerotic effect of the immunosuppressive drugs can be excluded [20]. However, it may be possible that differences may turn out to be significant in future studies with more patients for the study.

It is well recognized that smoking combined with immunosuppression has an especially severe potency to increase progression of macro-angiopathy [4]. Further variables were not evaluated on account of the small patient groups. Though the current smokers prior to SKPT discontinued smoking before transplantation, 1 year after SKPT the patients have initiated smoking again, but reduced their tobacco consumption after transplantation. The progression of macro-angiopathy was in the smoking group obviously higher than in the nonsmoking group. It can be speculated, that not only lowering blood pressure and more widespread administration of statins, but also cessation of smoking could reduce

cardiovascular mortality and possibly also influence chronic allograft vasculopathy [11,14,21].

We also evaluated the cancer indices in each group. In the literature the incidence of cancer after organ transplantation is reported to be approximately 10% [22]. In our study, one smoking patient developed lymphoma, two patients without smoking suffered from cancer (skin cancer and cancer of the bladder). No patient developed a lung cancer within the observation period.

The individual influence of metabolic control and renal insufficiency on the progression of macro-angiopathy is difficult to differentiate in smokers and nonsmokers. For better understanding of the respective effect of diabetes and uraemia in the progression of macro-angiopathy in type-1 diabetic patients, we compared the data of the SKPT patients with data of type-1 diabetic patients ($n = 12$, age 48 ± 9) who received a kidney transplant alone (KTA); five of them were smokers and seven nonsmokers. In summary, as regards the patients with KTA, the prevalence of vascular diseases prior to transplantation and the same at the end the of the observation period were higher in the KTA- than in the SKPT patients, but not in a statistically significant manner on account of on account of the small patient groups. The percentage increase of prevalence was higher only in the CAD when comparing smoking versus nonsmoking patients. All data of the KTA-patients were presented in table 5. It may be assumed that despite the rescued homeostasis of glucose by SKPT, the effect of previous diabetes with uraemia is long-lasting. Therefore, a reduction of the progression of macro-angiopathy on account of a functioning pancreas graft and also because of avoiding tobacco consumption, the same can be evaluated only after a longer period, probably after a period of at least 5–10 years [4]. The results for patient- and graft survival of our type-1 diabetic patients with SKPT were in part better than in other reports [23]. In the reported analysis of the UNOS data the one- and 5-year pancreas graft survivals were 85% and 74%. In our study the 1-year pancreas graft survival was 100% in both the groups with and without smoking. The 5-year pancreas graft survival was 75% in the smokers and 82% in the nonsmokers with graft function being surprisingly stable in both groups, the mean HbA1c levels were similarly at the start and the end of the observation period. In the same way, the kidney function remained stable during the same period, the decline of GFR was minimal, the Cr-Cl dropped by 8% in the smoking group and by 9% in the nonsmokers. However, we agree that patient groups in our study are small and therefore further studies with greater patient cohorts are warranted to confirm significant difference on patient- and graft survival in SKPT patients with and without smoking.

Table 5. Prevalence of cerebrovascular disease (CVD), coronary artery disease (CAD) and peripheral vascular disease (PVD) in patients with kidney transplantation alone (KTA) with and without smoking.

Prevalence of vascular disease (%)	Smokers ($n = 5$)	Nonsmokers ($n = 7$)
Prior to KTA		
CVD	40	28
CAD	40	28
PAD	40	28
End of the study		
CVD	60	43
CAD	80	43
PAD	60	43
Per cent increase		
CVD	50	54
CAD	100	54
PAD	50	54

In conclusion, smoking in patients with SKPT is associated with higher prevalence of vascular diseases as well as higher incidence of vascular complications. Additionally, mortality after SKPT tends to be higher in smoking patients. This is the first pilot study concerning the impact of smoking on macro-angiopathy in type-1 diabetic patients after SKPT. For the future, a multicentric study is necessary to confirm our results.

Authorship

GB: wrote text; PB, GB and BS: collected data; HP and OJ: analyzed data; RM: designed research/study.

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