

EFFECT OF SMOKING ON DEVELOPMENT OF NEW ONSET DIABETES MELLITUS AFTER TRANSPLANTATION (NODAT) OF KIDNEY

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Abstract

Purpose: Cigarette smoking has adverse effects on kidney transplant recipients, causing cardiovascular disease, kidney function impairment, and cancer. New onset diabetes mellitus after transplantation (NODAT) represents serious complication of transplantation of solid organs.

Methods: In the group of 252 patients after kidney transplantation, we identified smokers and current non-smokers (the patient who has not been smoking or who is ex smoker) for the period of minimum 24 months. In the monitored period of 12 months after transplantation, we detected presence of NODAT in both groups. The group contained only those patients who did not have diabetes mellitus (of type 1 and 2) at the time of kidney transplantation.

Results: The group of smokers was composed of 88 patients (34.9 %) and non-smokers 164 patients (65.1 %). The average age of smokers was 52 years \pm 12.4, and of current non-smokers it was 44.8 years \pm 12.8 ($P < 0.0001$). The smokers had significantly lower body mass index (BMI) at the time of kidney transplantation ($P = 0.0059$) and also 12 months after transplantation ($P = 0.0069$), lower weight gain 12 months after transplantation ($P = 0.0220$) and larger waist circumference 12 months after transplantation ($P < 0.0001$).

Conclusion: In our group, smoking had no effect on development of NODAT, the smokers had lower values of BMI and waist circumference, however, the guideline development group feels that, as for the general population, success of smoking cessation can be enhanced by offering structured smoking cessation programs.

Key words: smoking, NODAT, kidney transplantation

INTRODUCTION

The risk factors of cardiovascular diseases after kidney transplantation are eliminated by recovery of renal functions, however, new risks occur as for example disorder of glucose tolerance, diabetes mellitus, arterial hypertension, disorders of fat metabolism, and others. The newly diagnosed diabetes mellitus after transplantation (NODAT) represents serious and frequent complications of transplantation of solid organs (1). The incidence is between the limits of 4 % and 25 % depending on the transplanted organ, duration of monitoring of the patient, and the used immunosuppressive protocol (2, 3).

Disorder of glucose regulation in the patients after kidney transplantation results in 2–3 times higher cardiovascular morbidity and mortality when compared with non-diabetes patients, impairing the quality of life of the patients. The risk of development of cardiovascular diseases in the patients with NODAT is increased also by hyperlipoproteinemia, arterial hypertension or smoking. NODAT is connected with additional complications, as for example: rejection of the graft, recurrent infections, and worse long-term function of the graft (4, 5).

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Cigarette smoking has adverse effects on kidney transplant recipients, causing cardiovascular disease, kidney function impairment, and cancer. When smoking, the level of glycemia, insulin, and blood pressure is immediately increased. Chronic smoking damages endothelium of vessels, which results in insulin resistance, which further increases glycemia. Hyperglycemia in smokers is mostly permanent and is responsible for development of later diabetic complications. Heavy metals in the cigarette – mainly cadmium, also increase occurrence of diabetes mellitus (6).

The evidence of negative influence of smoking on the outcome of kidney transplantation is large and consistent stemming from well-adjusted multivariate analyses of observational data at low risk of bias. However, there was no consensus in the guideline development group to consider active smoking as contraindication for wait listing for transplantation. The major argument was that it is very difficult, if not impossible, to check the smoking status, and even if patients stopped smoking before transplantation, there is always the risk of relapse after transplantation. However, there was consensus to strongly recommend smoking cessation in kidney transplant candidates (7).

MATERIAL AND METHODS

In the group of 252 patients (of Central European origin) after primary kidney transplantation from post mortem donor (in the years 2003 – 2014) in the Transplan Center Martin, we identified smokers and current non-smokers (the patient who has not been smoking or who is exsmoker for the period of minimum 24 months). In the group of smokers, we recorded the number of smoked cigarettes/day. The information about smoking was included in the history and obtained from the patient and from the family relatives – the information were obtained with the help of medical nurses in the department and in the intensive care unit during hospitalization after kidney transplantation. In the monitored period of 12 months after transplantation, we detected presence of NODAT in both groups, that was diagnosed according to the ADA (American Diabetes Association's) criteria and oGTT was realized within the 10th – 12th week after transplantation and in the 12th month after transplantation. In addition to NODAT, in both monitored groups we recorded the age at the time of transplantation, the body mass index (BMI), the weight gain after kidney transplantation, the waist circumference 12 months after transplantation and glycated hemoglobin. We also discovered positive family history for NODAT (parents, brothers/sisters, and grandparents), as well as the cause of failure of native kidneys, and the immunosuppressive therapy, if any, which could affect the development of NODAT (in the period of 12 months before transplantation). In the monitored group, we further recorded the percentage share of the patients which took both pre-transplantation and post-transplantation hypolipidemic therapy (statin). The group was composed only of those patients who had no diabetes mellitus (type 1 and 2) at the time of kidney transplantation. The patients who had diagnosed, impaired glucose tolerance or impaired fasting glucose according to the oral glucose test as the screening before transplantation were also excluded from the research.

Monitoring was applied only in those patients who had tacrolimus in the immunosuppressive regime – i.e. the group was homogenous from the aspect of the administered immunosuppression. In the statistic evaluation, we applied the certified statistic program MedCalc version 13. 1. 2. and the following statistical analyses: Students t-test, chi-quadrat test, correlation coefficient. We find the value of $P < 0.05$ to be statistically significant.

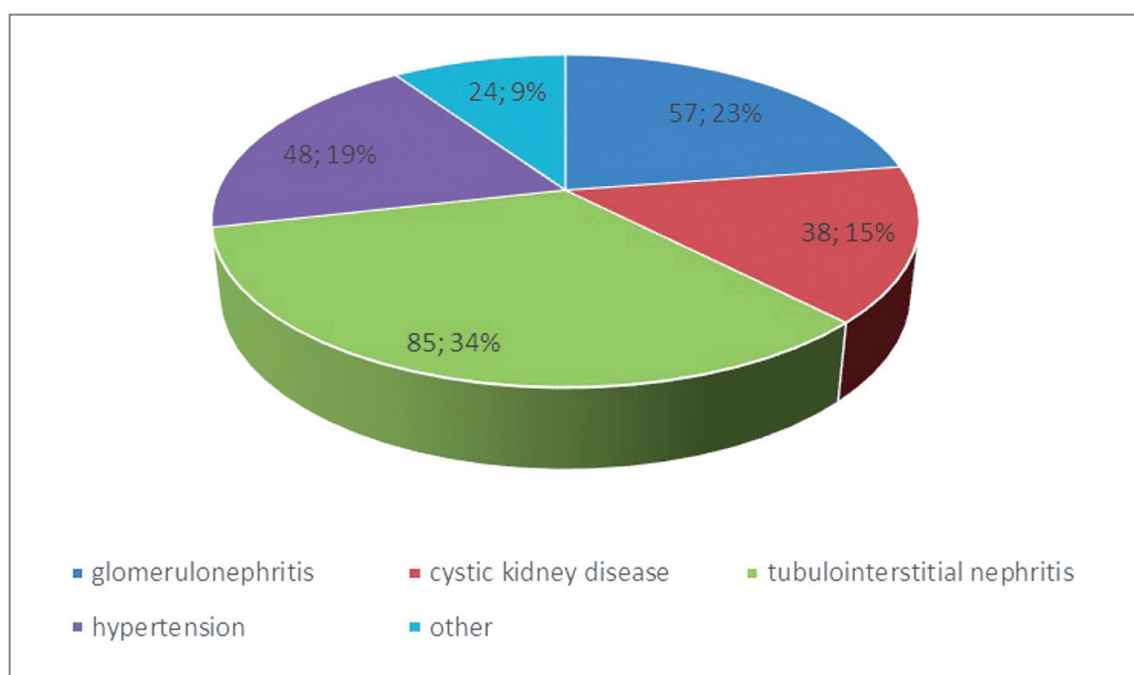
RESULTS

The group composed of 252 patients after primary kidney transplantation who had no diabetes mellitus of type 1 or 2 or prediabetes at the time of transplantation. The average age in the whole group was 48.4 years \pm 12.6. The group was homogenous from the aspect of the administered immunosuppression, and the results were not distorted by the immunosuppression (Tab. 1).

Table 1. Comparison of the group from the aspect of used immunosuppression

	non-smokers n = 164	smokers n = 88	P value
average level of TAC (ng/ml)	4.6 ± 0.7	4.7 ± 1.7	0.5115
average dose of prednisone/day (mg)	8.5 ± 2.5	8.7 ± 2.2	0.5288
average dose of MMF/day (mg)	883.4 ± 271.2	905.8 ± 170.5	0.4477
average dose of mycophenolate sodium/day (mg)	675.1 ± 281	730.8 ± 130	0.0796

Composition of the group according to the basic diagnose of kidney failure is shown in Fig. 1.

**Fig. 1** Composition of the group according to the basic diagnose of kidney failure

The group of smokers was composed of 88 patients (34.9 %) and current non-smokers of 164 patients (65.1 %). The average age of the current smokers was 52 years ± 12.4 and the current non-smokers 44.8 years ± 12.8 ($P < 0.0001$). The smokers had statistically significantly lower BMI at the time of kidney transplantation as well as 12 months after transplantation. The smokers had statistically significantly lower weight gain 12 months after transplantation versus the current non-smokers. The waist circumference 12 months after transplantation was significantly lower in the smokers. Development of NODAT in the monitored period in both groups was without any statistically significant difference. The value of glycated hemoglobin (HbA1c) was determined 6 and 12 months after kidney transplantation according to the recommendations of the American Diabetes Association, and no significant difference was found between the current non-smokers and smokers (Tab. 2).

Table 2. Characteristics of the group

	current non-smokers n = 164	smokers n = 88	P value
positive family history for DM 2 (%)	33,8	28,4	0.3816
taking immunosuppression in pre-transplantation period (%)	12	17	0.2728
using statins before transplantation (%)	25,6	25	0.9171
using statins after transplantation (%)	31,1	34,1	0.6160
age at the time of transplantation (years)	44.8 ± 12.8	52 ± 12.4	<0.0001
BMI at the time of transplantation (kg/m ²)	26.2 ± 4.8	24.5 ± 4.3	0.0059
BMI 12. months after transplantation (kg/m ²)	27.9 ± 5.1	26.1 ± 4.8	0.0069
weight gain 12 months after transplantation (kg)	5.2 ± 4.2	4.0 ± 3.4	0.0220
% weight gain 12 months after transplantation	9.1	3	0.0453
waist circumference 12 months after transplantation (cm)	98.6 ± 9.1	93 ± 8.5	<0.0001
HbA1c (%) 6 months after transplantation	5,7	5,6	0.9739
HbA1c (%) 12 months after transplantation	5,8	5,6	0.9482
NODAT in the monitored period (count/%)	74/45	45/51.1	0.6477
creatinine 12 months after transplantation (µmol/l)	136.1 ± 36.8	141.3 ± 41.3	0.3068
eGFR 12 months after transplantation (ml/s)	0.88 ± 0.28	0.82 ± 0.23	0.0863

The oGTT realised in the 10th to 12th week after transplantation diagnosed was NODAT at 33.6 % of patients, and the oGTT in the 12th month revealed 17.6 % patients. In the other patients, NODAT was diagnosed from normal collection of blood in fasting state after 8-hour fasting, and the diagnose was determined before realizing the oGTT. Impaired glucose tolerance or impaired fasting glycaemia was detected in immediate post-transplantation period (within 21 days following transplantation) in almost 90 % patients who then developed NODAT in the monitored period. We did not confirm statistically significant difference in NODAT incidence between both groups in observation period.

The group of smokers was composed of 47 patients who smoked less than 10 cigarettes/day and 41 patients who smoked on average more than 10 cigarettes/day. We detected no significant difference in the monitored parameters between the above subgroups (Tab. 3).

By applying the correlation coefficient we found out that the number of smoked cigarettes/day is irrelevant for the BMI value and the weight gain 12 months after kidney transplantation and development of NODAT (Tab. 4).

Table 3. Comparison of smokers according to the number of smoked cigarettes/day

	< 10 cigarettes/day n = 47	> 10 cigarettes/day n = 41	P value
Age at the time of transplantation (years)	50.7 ± 13.1	53.2 ± 11.7	0.3507
BMI at the time of transplantation (kg/m ²)	25.2 ± 4.2	24.9 ± 4.4	0.7445
BMI 12. months after transplantation (kg/m ²)	27.1 ± 4.7	26.6 ± 4.9	0.6268
weight gain after transplantation (kg)	4.1 ± 3.3	3.8 ± 3.4	0.6759
waist circumference 12 months after transplantation (cm)	93.8 ± 8.8	92.1 ± 8.2	0.3534
NODAT in the monitored period (count/%)	20/42.6	25/61	0.3533
creatinine 12 months after transplantation (μmol/l)	139.8 ± 38.2	142.8 ± 44.3	0.7338
eGFR 12 months after transplantation (μml/s)	0.86 ± 0.22	0.77 ± 0.24	0.0700

Table 4. Correlation between the number of smoked cigarettes and the monitored parameters

	Correlation coefficient r	95% Confidence interval for r	P value
BMI 12 months after transplantation (kg/m ²)	-0.03929	-0.2301 to 0.1545	0.6921
weight gain after transplantation (kg)	0.02699	-0.2223 to 0.2729	0.8337
development of NODAT	-0.04214	-0.2328 to 0.1517	0.6710

DISCUSSION

In our group, smoking was not found to be the risk factor for development of NODAT. However, the current non-smokers had at the time of transplantation and 12 months after transplantation higher value of BMI and weight gain, and the waist circumference 12 months after kidney transplantation was statistically significantly higher. The literature provides for no available analyses of smoking as a risk factor for NODAT in patients after kidney transplantation, however, many analyses are available regarding the non-transplanted population.

The IDEA study (of Slovak patients) confirms our results, when the evaluated population of smokers had lower waist circumference and lower prevalence of obesity than the group of non-smokers (8). Similar conclusions may be found also in the NEMESYS project where it was proved that smoking has ambiguous relation to obesity - maybe due to suppressed appetite and the tendency to reduce weight. (9, 10, 11). The NEMESYS project clearly states that the highest prevalence of abdominal obesity was found in ex-smokers, which is related to increased energetic intake, lower expenditure of energy in peace, and increased activity of lipoproteine lipase after smoking cessation (12). In the literature, we can often find the information that smokers, when compared with non-smokers, have higher weight and BMI values, however, the IDEA and NEMESYS projects confirmed that in the population of smokers, the prevalence of abdominal obesity is lower, which was proved also in our group. On contrary, the study carried out in China on randomly selected 13,463 males at the age of 35 and more years, did not confirm such data. The overall prevalence of centralobesity was 35.9 %. When compared with non-

smokers, only the ex-smokers had statistically significantly higher prevalence of abdominal obesity (13). Similarly as in our group, no correlation to the number of smoked cigarettes and the waist circumference was proved.

The American study of 27,000 males and almost 30,000 females evaluated the relationship between BMI and the waist circumference. Very strong relationship was found between the waist circumference and mortality due to CV diseases in patients with the same BMI values. It means that in the patients with the same BMI value, mortality due to CV diseases increases with the increasing waist measure. On contrary, in the patients with the same waist measure, mortality due to CV diseases was increased with higher BMI it was rather vice versa when in that group the mortality due to CV diseases was increased at lower BMI values. That data are proved by the authors to be connected with smoking, when smokers have lower BMI values, but at the same time the group of smokers shows higher mortality due to CV diseases (14).

However, the relationship between smoking and development of NODAT is not clearly confirmed. In spite of that, smoking of the patient after kidney transplantation is undesirable due to the high cardiovascular risk in such patients. A retrospective cohort study of 41,705 renal transplant recipients showed that smokers had increased risk of allograft loss (adjusted HR 1.46) and death (adjusted HR). Smoking cessation could improve renal survival (15, 16, 17). We believe that the basic reason that the incidence of NODAT in both monitored groups was comparable is the fact that the group of patients was homogenous from the aspect of immunosuppression. It is the immunosuppression therapy which affects the incidence of NODAT in the first year after transplantation. In the next following post-transplantation period, the incidence of NODAT is affected mainly by the life style and obesity. From the aspect of the weight gain, the most risky period is considered the period of the first 6 months after smoking cessation, and the increased risk may exist as long as 2 years from smoking cessation.

Smoking impairs also the course of complications of NODAT. Smoking causes oxidation stress and transformation of the growth factor $-\beta$, which leads to changes in the basal membrane of glomerulus. In the population of American diabetics, the occurrence of microalbuminuria and macroalbuminuria was significantly higher in the smokers (53 %) than in the non-smokers (20 %). By affecting the life style of diabetics/smokers, we may avoid the terminal stage of chronic renal disease or at least postpone the necessary elimination therapy (18). Several analyses confirmed that smoking has significant effect on the HbA1C level (19). The substances which cause increased HbA1C levels in the smokers/diabetics are not precisely identified until today. Currently, discussion has started that the higher HbA1C levels may be caused by the nicotine itself because nicotine may increase the HbA1C level almost by 34 %. Obviously, the higher number of the smoked cigarettes, the higher the HbA1C value. However, the use of nicotine plasters, nicotine chewing gums, and other aids in dishabituating therapy still remains a question. However, the benefits of non-smoking may prevail the risks of using such products, mainly due to short-term use thereof (20). Smoking is a strong risk factor for premature atherosclerosis, atherothrombotic events and cardio-vascular death. Curiously, smokers with acute myocardial infarction have lower short-term mortality rates than nonsmokers. The "smoker's paradox" can be explained by differences in baseline risk factors, and not smoking status per se, mainly because smokers suffer their myocardial infarctions on average a decade earlier than nonsmokers (21).

CONCLUSION

In our group, smoking had no effect on development of NODAT, the smokers had lower values of BMI and waist circumference, however, the guideline development group feels that, as for the general population, success of smoking cessation can be enhanced by offering structured smoking cessation programs (7).

In the most risky period for weight gain (the first 6 months after smoking cessation) it is important to educate the patient about the change of life style, diet, and particularly about the

necessity of physical activity for minimum 20 minutes daily. It is a positive fact that exsmokers have similar behaviour models (life style – diet, physical activity, etc.) as non-smokers (22). It suggests that dishabituation from smoking is connected with positive change in the behaviour and care of the patient's health (19). Screening of risk factors for diabetes mellitus should be done even before placing the patient on the waiting list and it is advisable to carry out the oral glucose tolerance test (oGTT) also in patients with physiological levels of fasting glycemia (23, 24) – the key role in education is played by nephrologists in dialyzing centers, in cooperation with diabetologists.

REFERENCES

1. Yates CJ, Furlanosa S, Hjelmæsæth J, Colmana PG, Cohneyb, SJ. New-Onset Diabetes After Kidney Transplantation—Changes and Challenges. *American Journal of Transplantation* 2012; 12: 820–828.
2. Dedinská I, Laca L, Miklušica J, Galajda P, Mokáň M. Twelve-Month and Five-Year Analyses of Risk Factors for New-Onset Diabetes After Transplantation in a Group of Patients Homogeneous for Immunosuppression. *Transplantation Proceedings* 2015; 47: 1831-1839 (in press).
3. Chakkera HA, Weil EJ, Phuong-Thu P, Pomeroy J, Knowler WC. Can New-Onset Diabetes After Kidney Transplant Be Prevented? *Diabetes Care* 2013; 36:1406–1412.
4. Hjelmæsæth J, Hartmann A, Leivestad T. The impact of early-diagnosed new-onset post-transplantation diabetes mellitus on survival and major cardiac events. *Kidney Int.* 2006; 69: 588–595.
5. Grandtnerová, Laca L, Gábor D, Gregová E, Korónyi S: Folic acid supplementation and homocyst(e)ine level in renal transplant recipients. *Transplantation Proceedings* 2001; 33 (1-2): 2049-2050.
6. Ilavská A. Diabetes mellitus a smoking. *Bedeker zdravia* 2006; [online] <http://www.bedekerzdravia.sk/?main=article&id=157>
7. ERBP GUIDELINE ON THE MANAGEMENT AND EVALUATION OF THE KIDNEY DONOR AND RECIPIENT Nephrol Dial Transplant (2013) 28: ii1–ii71doi: 10.1093/ndt/gft218
8. Dukát A. Prevalencia abdominálnej obezity na Slovensku štúdia IDEA Slovakia. *Vnitř Lék* 2007; 53 (4): 326-330.
9. Alberti KG, Zimmet PR, Shaw J. IDF Epidemiology Task Force Consensus Group. The metabolic syndrome – a new worldwide definition. *Lancet* 2005; 366: 1059–1062.
10. Lakka HM. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA* 2002; 288: 2709–2713.
11. Lietava J. Projekt Nemesys – skríning metabolického syndrómu u ambulantných pacientov. *Interná Med* 2006; 6 (12): 685–689.
12. Ferrara CM. Weight gain and adipose tissue metabolism after smoking cessation in women. *Int J Obes Relat Metab Disord* 2001; 25: 1322–1326.
13. Xu F, Yin XM, Wang Y. The association between amount of cigarettes smoked and overweight, central obesity among Chinese adults in Nanjing, China. 2007; 16 (2): 240-247.
14. Bigaard J. Waist Circumference, BMI, Smoking, and Mortality in Middle-Aged Men and Women. *Obesity research journal* 2003; 11: 895-903.
15. Hurst FP, Altieri M, Patel PP, et al. Effect of Smoking on kidney transplant outcomes: analysis of the United States Renal Data System. *Transplantation* 2011; 92: 1101.
16. Mercado C, Jaimes EA. Cigarette smoking as a risk factor for atherosclerosis and renal disease: novel pathogenic insights. *CurrHypertens Rep* 2007; 9: 66.
17. Hornum M, Lindahl JP, Jenssen T, Feldt-Rasmussen B. Diagnosis, management and treatment of glucometabolic disorders emerging after kidney transplantation A position statement from the Nordic Transplantation Societies. *Transplant International* 2013; 26: 1049–1060
18. Klien R, Klien B, Moss S. Epidemiology of proliferative diabetes retinopathy. *Diabetes care.* 1992; 15: 1875-1891.
19. Nilsson PM, Gudbjörnsdóttir S, Cederholm J. Smoking is associated with increased HbA1c values and microalbuminuria in patients with diabetes – data from the National Diabetes Register in Sweden. *Diabetes & Metabolism* 2004; 30 (3): 261-268.

20. Smoking Main Cause of Complications in Diabetes. Washington, D.C., American Chemical Society 2010 [online]: [purchasehttp://www.disabledworld.com/health/diabetes/smoking-diabetes.php](http://www.disabledworld.com/health/diabetes/smoking-diabetes.php)
21. Blinc A. The misleading "smoker's paradox". E-Journal of Cardiology Practice 2005; 4(15): dostupné online [<http://www.escardio.org/Journals/E-Journal-of-Cardiology-Practice/Volume-4/vol4n15-Title-The-misleading-smoker-s-paradox>]
22. Vojtková J., Ďurdík P., Michnová Z., Turčan T., Čiljaková M. Exhaled carbon monoxide in adolescents with diabetic cardiovascular autonomic neuropathy. J Pediatr EndocrinolMetab. 2014; 27 (7-8): 709-715.
23. Laca I., Olejník J., Vician M et al. The effect of occlusive techniques on the short-term prognosis after liver resections. Hepato-Gastroenterology, 2006; 53 (69): 576-579.
24. Zelenák K., Šinák I., Janík J., Laca I et al. Bleeding in acute pancreatitis treated by transcatheter arterial embolization with ethylen-vinyl alcohol copolymer (ONYX). VASA-Journal of Vascular Diseases, 2012; 41 (5): 380-382.

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