

Impact of Cigarette Smoking on Kidney Transplant Recipients

A Systematic Review

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Keywords. Cigarette, smoking,
renal transplantation, graft
survival, mortality

Introduction. Cigarette smoking has adverse effects on kidney transplant recipients, causing cardiovascular disease, kidney function impairment, and cancer. However, there are surprisingly few studies on the impact of cigarette smoking among kidney transplant recipients and its consequences after transplantation. We performed a systematic review of the literature to identify the effects of cigarette smoking on patient and graft survival rates among kidney transplant recipients.

Materials and Methods. We searched the PubMed from 1968 to 2009 to identify studies on the effect of cigarette smoking on kidney transplant recipients, using the following keywords: *kidney transplantation, cigarette, smoking, tobacco, and nicotine*. The electronic and manual searches yielded 357 articles, of which 39 were considered potentially relevant by titles and abstracts and were selected for full text review. Twenty-seven irrelevant reports were excluded.

Results. A total of 12 papers were selected for review, comprising of 1801 kidney transplant recipients with a history of smoking. The impact of cigarette smoking on kidney recipient survival was only evaluated by 6 studies and the relative risk of smoking for death was available in 3 reports, varying between 0.8 and 2.2. Cigarette smoking was an independent risk factor for patient death. In addition, on univariable and multivariable analyses, graft survival correlated with a history of cigarette smoking and the relative risk for graft failure ranged from 1.06 to 2.3.

Conclusions. Cigarette smoking was associated with an increased risk of death and graft loss. Therefore, every attempt should be made to encourage kidney transplant candidates to stop smoking.

IJKD 2011;5:141-8
www.ijkd.org

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of mortality among kidney transplant recipients.^{1,2} In addition, smoking is a major potentially modifiable or avoidable risk factor for CVD.^{3,4} Ponticelli and colleagues⁵ reported that smoking was associated with a higher risk of CVD (relative risk [RR], 1.3; $P = .02$) in 864 adults kidney transplant recipients. Furthermore, Kasiske and coworkers^{6,7} found that

kidney transplant smokers had a greater risk of ischemic heart disease (RR, 1.95) compared with nonsmoking recipients. Recipient smokers have a significantly shorter mean survival due to mortality from CVD, in which smoking played an important contributing role.^{8,9} In addition, established cardiovascular risk factors other than smoking, such as hypertension, diabetes mellitus, and dyslipidemia, are more frequent in kidney

transplant recipients than in the general population. These risk factors increase the risk of CVD among kidney transplant recipients and decrease patient and graft survivals.¹⁰

Cancer, the second cause of death in kidney transplant recipients, is another consequence of smoking.¹¹ Risk factors for malignancy after transplantation include factors common to the general population, such as age, smoking habits, and sun exposure.¹² For example, a series of 1500 kidney transplant recipients showed that age greater than 45 years old ($P = .007$) and cigarette smoking ($P = .02$) were significantly associated with an elevated risk of malignancy.¹³ In a series of 84 heart transplants, cigarette smoking was associated with reduced recipient survival and increased risk of posttransplant cancer.¹⁴ Finally, cigarette smoking is also a known major risk factor for the development of chronic obstructive lung disease, with 90% of mortality from chronic obstructive lung disease directly attributable to smoking.¹⁵ Therefore, smoking can lead to reduced patient survival by causing lung disease.

The prevalence of smoking among kidney transplant recipients is 25% and 35% to 40% in American and European patients, respectively.^{16,17} On the other hand, cigarette smoking is the world's major cause of premature mortality responsible for an estimated 5 million deaths each year.¹⁸ Although the adverse effects of smoking in the nontransplant setting are well known, its impact on patient and graft survival after kidney transplantation remains unclear. There are, however, surprisingly few studies addressing cigarette smoking among

kidney transplant recipients. Thus, we performed a systematic review of the literature to identify the effects of cigarette smoking on patient and graft survival rates among kidney transplant recipients.

MATERIALS AND METHODS

We searched the PubMed database from 1968 to 2009 to identify studies that had reported the effect of cigarette smoking on kidney transplant recipients. Our keywords included *kidney transplantation*, *cigarette*, *smoking*, *tobacco*, and *nicotine* and their synonyms. To identify additional relevant articles, bibliographies of qualitative topic reviews and the identified articles were also searched. Duplicated publications were discarded. We restricted our search to human studies and placed no restrictions on language. Our review aimed to address two specific questions: (1) What is the effect of cigarette smoking on kidney allograft survival? (2) What is the effect of cigarette smoking on the kidney transplant recipient survival?

There were not enough case-control and cohort studies reporting adjusted RRs and 95% confidence intervals (95% CI) of all-cause mortality and graft failure among kidney transplant smokers relative to nonsmoker patients (Table 1); therefore, we could not assess the pooled adjusted RR and 95% CI of these endpoints in a meta-analysis. Table 1 shows the characteristics of studies included in this review.^{1,4,8,9,16,17,19-24}

RESULTS

The electronic and manual searches yielded 357 papers by titles and abstracts, of which 39 were

Table 1. Baseline Characteristics of Studies Included in This Review

| Authors | Year | Country | Study Design | Number of Patients | |
|---|------|-------------|----------------------|--------------------|---------|
| | | | | All | Smokers |
| Arend et al ¹ | 1997 | Netherlands | Retrospective cohort | 804 | 394 |
| Cosio et al ⁶ | 1999 | US | Retrospective cohort | 523 | 147 |
| Kasiske and Klinger ¹⁷ | 2000 | US | Retrospective cohort | 1334 | 330 |
| Matas et al ²¹ | 2001 | US | Retrospective cohort | 2540 | ...* |
| Sung et al ¹⁹ | 2001 | US | Retrospective cohort | 645 | 156 |
| Woo et al ⁹ | 2002 | UK | Retrospective cohort | 515 | 234 |
| Yavuz et al ¹⁶ | 2004 | Turkey | Retrospective cohort | 226 | 97 |
| Kheradmand and Shahbazian ²⁰ | 2005 | Iran | Retrospective cohort | 199 | 41 |
| Zitt et al ²³ | 2007 | Austria | Prospective cohort | 76 | 76 |
| Suneja et al ²⁴ | 2007 | US | Case report | 1 | 1 |
| Banas et al ⁴ | 2008 | Germany | Cross-sectional | 264 | 156 |
| Mohamed et al ²² | 2009 | India | Retrospective cohort | 303 | 169 |

*Number of patients with a history of smoking was not provided in the article.

considered potentially relevant and were selected for full text review. Twenty-seven irrelevant reports were excluded. After full text review, 9 retrospective cohort studies, 1 prospective cohort study, 1 cross-sectional study, and 1 case report were selected for our review (Table 1). Eighteen hundred and one patients with a history of smoking before kidney transplantation (ex-smoker) or after kidney transplantation were included in this review.

The impact of cigarette smoking on kidney recipient survival had been evaluated by 6 studies,^{1,8,9,16,17,19} and the RR of smoking for death was available in 3 reports, varying from 0.8 to 2.2.^{1,9,17} Cigarette smoking was an independent risk factor for patient survival, and kidney transplant recipients with a smoking history had a significantly shorter survival (Table 2). However, Yavuz and colleagues, who only reported univariable analysis, did not find a decreased patient survival in smokers after transplantation.¹⁶ Univariable^{19,20} and multivariable^{8,9,17,19,21} analyses showed that graft survival correlated with a history of cigarette smoking, and the RR for graft failure ranged from 1.06 to 2.3 (Table 2). In contrast, two retrospective cohort studies showed that cigarette smoking was not a risk factor for graft failure on univariable analysis.^{16,22} However, it should be noted that the number of patients included in these studies was relatively small (Table 1).

Kasiske and Klinger reported the prevalence of cigarette smoking and its impact on patient and

graft survival in a large cohort of kidney transplant recipients.¹⁷ The total number of pack-years smoked reported at the time of kidney transplantation was a stronger predictor for transplant outcomes. In univariable analysis, smoking more than 25 pack-years at the time of kidney transplantation was associated with increased graft loss and a higher mortality rate (Table 2). After adjusting for multiple predictors of kidney allograft loss, smoking more than 25 pack-years (compared to smoking less than 25 pack-years or no smoking) was associated with a 30% higher risk of graft loss (Table 1). Having quit smoking more than 5 year prior transplantation reduced the relative risk of kidney allograft loss by 34% (Table 2). This increased graft loss was largely due to the increased mortality.¹⁷ The total consumption of cigarette smoking was associated with CVD; for example, the RR of smoking 11 to 25 pack-years at the time of transplantation was 1.56 (95% CI, 1.06 to 2.31; $P = .02$), whereas that of smoking more than 25 pack-years was 2.14 (95% CI, 1.49 to 3.08; $P < .001$). The incidence of cancer was also increased by cigarette smoking and its RR was 1.91 (95% CI, 1.05 to 3.48; $P = .03$).¹⁷ The adjusted RR for lung neoplasms with smoking greater than 25 pack-years was 8.48 (95% CI, 1.64 to 43.92; $P = .01$). In contrast, cigarette smoking had no statistically significant effect on cancers other than lung cancer.¹⁷

Zitt and associates²³ examined 76 kidney allograft biopsies performed more than 1 year after kidney

Table 2. Impact of Cigarette Smoking on Graft and Patient Survival Rates*

| Authors | Graft Survival | | | | Patient Survival | | | |
|---|-----------------|------------------------|--------------|--------|------------------|------------------------|--------------|------|
| | Univariable P | Multivariable Analysis | | | Univariable P | Multivariable Analysis | | |
| | | RR | 95% CI | P | | RR | 95% CI | P |
| Cosio et al ⁸ | ... | ... | ... | .02 | .004 | ... | ... | .009 |
| Arend et al ¹ | | | | | | | | |
| < 1 year after transplant | ... | ... | ... | ... | ... | 0.7 | 0.3 to 1.5 | ... |
| > 1 year after transplant | ... | ... | ... | ... | ... | 2.2 | 1.4 to 3.7 | .002 |
| Kasiske and Klinger ¹⁷ | | | | | | | | |
| 1 to 10 pack-years | ... | 1.06 | 0.83 to 1.34 | .65 | ... | 0.82 | 0.58 to 1.16 | .27 |
| 11 to 25 pack-years | ... | 1.12 | 0.87 to 1.42 | .38 | ... | 1.16 | 0.84 to 1.61 | .36 |
| > 25 pack-years | ... | 1.3 | 1.04 to 1.63 | .02 | ... | 1.42 | 1.08 to 1.87 | .01 |
| Quit > 5 years pretransplant | ... | 0.66 | 0.52 to 0.85 | < .001 | ... | 0.71 | 0.52 to 0.97 | .03 |
| Matas et al ²¹ | ... | 2.1 | ... | < .001 | ... | ... | ... | ... |
| Sung et al ¹⁹ | .007 | 2.3 | ... | < .001 | ... | ... | ... | .007 |
| Woo et al ⁹ | ... | 1.81 | ... | ... | ... | 1.48 | ... | ... |
| Yavuz et al ¹⁶ | .10 | ... | ... | ... | .20 | ... | ... | ... |
| Kheradmand and Shahbazian ²⁰ | .01 | ... | ... | ... | ... | ... | ... | ... |
| Mohamed et al ²² | .35 | ... | ... | ... | ... | ... | ... | ... |

*RR indicates relative risk and CI, confidence intervals. Ellipses indicate that data were not available.

transplantation. A kidney biopsy was done in 39% of smokers and 24% of nonsmokers ($P = .02$), and smokers underwent biopsy 1.5 years earlier on average. Among patients who underwent biopsy, current smokers tended to develop graft failure (33.3% versus 21.2%, $P = .25$). Severity of vascular intimal fibrous thickening was associated with cigarette smoking ($P = .004$); thus, the main allograft lesion associated with smoking is fibrous intimal thickening of small arteries.²³

In a cross-sectional single-center study, Banas and coworkers showed that kidney transplantation was a strong incentive for patients to stop smoking. Reasons for changes in smoking behavior after kidney transplantation may be an intense contact of the patients with their physicians, the fear of a premature loss of the transplant organ with continued smoking, and the psychological support during posttransplant patient care.⁴

Suneja and colleagues reported a 48-year-old woman with a long-term history of smoking who underwent cadaveric kidney transplantation. A kidney biopsy due to progressive deterioration of kidney function 11 years after transplantation showed features of nodular glomerulosclerosis. Other causes of nodular glomerulosclerosis were excluded. The authors speculated that long exposure to smoking might be the etiologic factor for nodular glomerulosclerosis in the kidney allograft of the patient.²⁴

DISCUSSION

Our overview shows that few studies have been performed to assess the effect of cigarette smoking on kidney transplant outcomes; therefore, limited data are available for increasing the knowledge of physicians in terms of adverse effects of smoking habits among kidney transplant recipients. Interestingly, there are only 6 reports about the impact of cigarette smoking on patient survival and 8 studies about its effect on kidney allograft survival (Table 2).

Cigarette smoking harms almost every organ in the body including the heart, lungs, immune system, and kidneys. Smoking may also have adverse effects on kidney function.²⁵ Indeed, studies in nontransplant populations have shown that smoking has a negative impact on kidney function.^{26,27} Theoretically, cigarette smoking can lead to poorer survival of the transplanted

kidney, partly due to its role in atherosclerosis, endothelial dysfunction, and vascular disease.²⁸ Tobacco may result in microvascular changes in the allograft, declined renal plasma flow, increased synthesis of endothelin-1, enhanced platelet aggregation, reduced generation of the vasodilator endothelial nitric oxide, and increased thickness of renal artery.^{29,30} Chronic cigarette smoking may increase proteinuria.³⁰ Nicotine also stimulates the sympathetic nervous system,³¹ resulting in acute renal vasoconstriction, which seems to be irreversible in smokers.^{26,27} Cigarette smoke itself has large amounts of free radicals and induces free radical production.^{23,32} However, there are few studies^{8,9,16,17,19-22} aimed to answer this important question: does cigarette smoking affect graft survival rate among kidney transplant recipients?

Sung and colleagues¹⁹ found that cigarette smoking prior to receiving a kidney transplant was associated with 2.3 times higher risk of graft loss. Matas and coworkers also showed that pretransplant smoking was an important risk factor of a poorer long-term graft survival among recipients with 1-year graft survival (RR, 2.1).²¹ A Cox multivariate analysis of graft survival identified cigarette smoking as an independent predictor of graft failure, and graft survival was significantly lower in smoker patients than in nonsmoker recipients (RR, 1.8).⁹ In a large prospective study in kidney transplant recipients, smoking was also a risk factor for graft loss in the unadjusted and adjusted analyses.³³ Interestingly, the magnitude of the adverse effect of smoking on graft survival in kidney transplant recipients was similar to that of diabetic patients.⁸ On the other hand, the total number of packs of cigarettes smoked per year at the time of transplantation was a better predictor for graft loss; smoking more than 25 pack-years (compared to smoking less than 25 pack-years or no history of smoking) was associated with a 30% higher risk of graft failure.¹⁷

In contrast, Yavuz and associates failed, in an univariable analysis, to find a correlation of graft survival with a history of cigarette smoking.¹⁶ A similar conclusion was reached in the study by Mohamed and coworkers.²² However, these studies only evaluated the graft survival based on a relatively small study population and a short follow-up, applying only univariable analysis. A larger sample size and longer observation of the

adverse effect of cigarette smoking on graft survival might have changed their results.

Most of the negative effects of smoking on graft survival is largely due to increased mortality¹⁷ and no correlation has been found between smoking and the rate of acute rejection episodes after kidney transplantation.²⁰ In contrast, some authors believe that adverse effects of smoking on graft survival is not explained by increased number of rejection episodes or patient's death, suggesting aggravation of chronic allograft nephropathy.^{23,34} Zitt and coworkers, in a study that included data on allograft histology, demonstrated persistent smoking after transplantation caused vascular fibrous intimal thickening in kidney allografts, which could be a risk factor for the development of chronic allograft nephropathy.²³ Suneja and colleagues reported an association between long exposure to smoking and nodular glomerulosclerosis in a kidney allograft.²⁴ Finally, having quit smoking more than 5 years prior to kidney transplantation decreased the relative risk of graft loss by 34%.¹⁷ However, in a study with a small number of kidney transplant recipients, no correlation was found between quitting smoking and graft loss.²⁰

It is of interest that kidneys from donors with a history of cigarette smoking prior kidney transplantation have lower graft survival rates (hazard ratio, 1.05; $P < .05$).²⁸ A similar conclusion was reported in the study by Cosio and coworkers.⁸ In contrast, based on the United Network for Organ Sharing data in 1995 and 1998 and the experience of the Regional Organ Procurement Agency of Southern California, Los Angeles, previous studies by Cho and colleagues showed graft survival was not affected if the donor had a history of cigarette smoking.³⁵⁻³⁷

Cigarette smoking has adverse effects on humans, causing cardiovascular, pulmonary or liver disorders, and cancer. Combination of smoking and kidney transplantation may increase the risk of complications resulted from either of these disorders.⁸ In particular, smoking itself is the main cause of atherosclerosis and it is one of the well-known causes of many systemic diseases and factors increasing mortality in kidney transplant recipients.³⁰ Cigarette smokers had a significantly shorter survival after transplantation, because most kidney transplant recipients died of CVD in which smoking played a contributing role.^{8,9} However,

there are few studies on evaluation of the effect of cigarette smoking on the survival rate of kidney recipients.^{1,8,9,16,17,19}

Cigarette smoking roughly doubled the risk of mortality beyond the first year after transplantation, similarly to its effect in the general population.¹ Kidney transplant recipients had significantly higher mortality rates compared to individuals without a kidney disease, largely due to CVD.⁸ By univariable and multivariable analyses, recipient survival, censored at the time of graft failure, correlated with a history of cigarette smoking prior to transplantation ($P = .004$).⁸ Kasiske and Klinger, in a study among kidney transplant recipients, found that cigarette smoking was associated with decreased patient survival.¹⁷ In addition, the total number of pack-years smoked by the time of transplantation was an important predictor for patient outcomes. In a Cox multivariable analysis, smoking more than 25 pack-years at the time of transplantation was associated with an increased risk of death in kidney transplant recipients.¹⁷ The effects of smoking appear to dissipate 5 years after quitting. These data suggest that greater attempts to encourage recipients to quit smoking before transplantation may reduce patient death rates.¹⁷ Furthermore, Woo and associates showed a high prevalence of electrocardiographic abnormalities and CVD risk factors in kidney transplant recipients, and smoking itself was an independent risk factor (hazard ratio, 1.81) for patient survival.⁹ Cardiovascular disease and cerebrovascular disease were major causes of increased mortality in kidney transplant recipients.³⁸ It is also recognized that smokers have a higher risk of stroke than nonsmokers,⁸ and carotid plaque was associated with current cigarette smoking.³⁸ Importantly, history of cigarette smoking in donors was also associated with decreased recipient survival (hazard ratio, 1.06; $P < .05$).²⁸

Smoking habits are also known to be a major cause of coronary artery disease and vascular disorders.⁸ Kidney transplant recipients are at increased risk for atherosclerosis after transplantation due to several risk factors of arteriosclerosis such as hypertension, dyslipidemia, and posttransplant diabetes mellitus; on the other hand, smoking acts synergistically with these other risk factors to greatly increase the risk of CVD.^{8,10} These traditional cardiovascular risk factors are more frequent in kidney transplant recipients than the general

population.¹⁰ Individuals in this population are also more likely to be male, of a lower socioeconomic status, and have a higher alcohol intake.^{39,40} In addition, Ponticelli and colleagues found, in a series of 864 adults kidney transplants, a higher risk of CVD after transplantation with smoking (RR, 1.29; $P = .02$).⁵ In another study of 210 cardiac transplant patients, smoking habits correlated significantly with the occurrence of coronary artery disease after transplantation.⁴¹ Kidney transplant recipients who were smoking for more than 25 pack-years had a 2-fold greater risk of CVD than nonsmokers.¹⁷ Cigarette smoking contributes to CVD in a number of ways such as increasing the heart rate and blood pressure via activation of catecholamines and β -adrenergic mechanisms.³⁰

Cigarette smoking is known to cause cancer in the general population. It is not surprising that the risk of malignancy in immunocompromised kidney recipients is increased by smoking. In a study of smoking among 1334 kidney transplant recipients, the incidence of cancer was increased in smokers compared to nonsmokers (RR, 1.9; $P = .03$).¹⁷ Furthermore, in a series of 84 heart transplant recipients, cigarette smoking was a risk factor for development of malignancy ($P = .0001$).¹⁴ In other series of 1500 kidney transplant recipients showed that age greater than 45 years ($P = .007$) and cigarette smoking ($P = .02$) were significantly associated with an increased risk of cancer.¹³ Efforts to reduce immunosuppression, particularly for kidney transplant recipients of age 45 years of age or greater at transplantation, along with a greater effort to discourage cigarette smoking, may help decrease the risk of tumor among kidney transplant recipients.⁴² The incidence of posttransplant malignancy also correlated with the total number of cigarettes smoked, for example the adjusted RR for lung cancers with smoking 1 to 10 pack-years was 1.13; with 11 to 25 pack-years, it was 1.32; and with greater than 25 pack-years, it was 8.48.¹⁷ Smoking has been reported to adversely affect the outcome of patients undergoing liver transplantation. In a study of 237 liver transplant patients, smokers had a higher incidence of ascites and encephalopathy.⁴³ In another series of 136 liver recipients, all-cause mortality was greater in smokers compared to nonsmoker individuals ($P = .04$). In addition, a multivariable analysis showed that smoking roughly doubled the risk of

patient death (hazard ratio, 2.2; $P = .03$), especially due to cardiovascular-related mortality ($P = .01$).¹⁸ Cigarette smoking was associated with a higher risk for developing vascular complications after liver transplantation. Quitting smoking at least 2 years before liver transplantation can decline the risk for vascular complications and reduce their morbidity after liver transplantation.⁴³

The harmful effects of smoking cigarette after heart transplantation are well established. For example, in a multivariable analysis among heart transplant patients, smoking habits (odds ratio, 5.2) was an independent predictor of lower health.⁴⁴ In another study of 288 heart transplantation showed a poorer prognosis and a longer recovery unit stay.⁴⁵ On multivariable analysis in 136 patients who underwent lung and heart-lung transplantation, smoking history was associated with a higher risk for rapid loss of kidney function after transplantation.⁴⁶

Finally, in 35 type 1 diabetic patients with simultaneous kidney-pancreas transplantation, cigarette smoking was associated with a higher rate of vascular complications (stroke, myocardial infarction, and amputation) and a lower patient survival rate when compared with nonsmokers.⁴⁷

CONCLUSIONS

No large-scale study has addressed the impact of smoking on kidney transplant outcomes. Unfortunately, the potential impact of cigarette smoking in kidney transplant recipients has received little attention. According to a limited number of retrospective and cohort studies, cigarette smoking is associated with an increased risk of death and graft loss. Therefore, every attempt should be made to encourage kidney transplant candidates to stop smoking.

CONFLICT OF INTEREST

None declared.

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Received March 2010
Revised November 2010
Accepted January 2011

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